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DR. MORRIS: I deem it a privilege to open this Seminar of Regional Medical Consultants. May I introduce one of the founders of the Jewish National Home for Asthmatic Children, our President. She has guided and directed the destiny of the Home since 1907. Hers has been a half-century of devoted service. Ladies and gentlemen, Mrs. Fannie E. Lorber.

MRS. LORBER: Thank you, Dr. Morris, for your kind words. I extend a warm welcome to you all. As you know, the home specializes in the treatment of children afflicted with intractable asthma. You, our Regional Medical Consultants, are an important part of our program of service, which extends into almost every community of our nation. We thank you for your participation in this Seminar.

DR. MORRIS: Thank you, Madame President. May I present the General Chairman of the Seminar, Dr. Harold Tuft.

DR. TUFT: Thank you, Dr. Morris, for your introduction. Dr. J. M. Morris is a functioning Board member and our Dental Consultant. It is a pleasure to welcome you. May I introduce Dr. M. Murray Peshkin, our Chief Medical Consultant, who will describe the rehabilitation program.

## DEVELOPMENT OF THE REHABILITATION PROGRAM

DR. PESHKIN: Mr. Chairman, our beloved President, and friends. I feel that the timeliness of this report warrants my presenting the data in detail.

The pioneer work of the National Home for Jewish Children at Denver was inaugurated fifty years ago in the interests of well children of the tubercular poor.

During 1930, the *American Journal of Diseases of Children* published

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Proceedings of seminar held at the Jewish National Home for Asthmatic Children, Denver, Colorado, January 30-31, 1957.

my paper, "Asthma in Children—A Plea for a 'Home' as a Restorative Measure." Chronic bronchial asthma in children who do not respond to modern medical treatment in their own community is one of the most serious forms of allergy. It is most severe during the early school years, and may cause structural changes leading to "chronic pulmonary crippling." At that time there was nowhere in this country an institution where the advantages of favorable environment could be devoted to the rehabilitation of children suffering from refractory asthma.

Later, I clearly recognized the need to separate a child from its parents. I learned that asthma was not always a matter of climate. Placing the desperately-ill asthmatic child in a hospital, although within a stone's throw from his own home, often, within a few days, dramatically relieved the asthma. This favorable response might also occur during the height of the pollen season. Relief was also obtained for children who had resided in other homes that had been made allergen-free.

At that time, I was continuously searching for an environmental physical allergen. It was not until 1935 that it occurred to me that it was remarkable that such severe, apparently pathological lesions, could clear so quickly. The period of hospital residence did not extend beyond two months. However, a visit by the mother could cause exacerbations although the child was following a strict anti-allergic regime. When the child returned home the flare-up of asthma often occurred within hours. I realized then that emotional climate was probably the most important etiological factor in these patients. Separation from all the members of the family, including the mother, "parentectomy," as I termed it, was advocated.

As a result, I initiated, in 1940, at the invitation of the Board of Directors of the National Home, a program designed to rehabilitate the child with intractable asthma. Since 1940 the program of separation has been implemented. The procedure of complete psychological as well as physical separation often takes months.

The rehabilitation treatment at Denver has been so consistently effective that several years ago the Home focused its entire attention on the problems of the child with intractable asthma. It expanded its facilities to care for 150 children and changed its name to The Jewish National Home for Asthmatic Children. The medical, psychiatric and sociological programs have been improved and expanded.

The average period of treatment for the type of child admitted to the Home is two years. With this program 90 per cent of the children are essentially asthma-free. Surprisingly enough, pollen therapy may not be necessary in some specifically pollen-sensitive children. Those patients originally from Metropolitan New York are studied in a follow-up clinic for a number of years after their return to their homes.

After the children have been living with their families for one year or more, more than 80 per cent of them are either asthma-free or are essentially so. These data can be correlated with what you will hear from Dr. Abramson concerning the concept of parental engulfment. The treatment at the Home strives to develop in the children independence of thought and action, within the framework of the program. The future program includes a more detailed study of the psychodynamic mechanisms in bronchial asthma.

Parentectomy may be viewed as a mechanism that can be included in evidence for the "engulfment theory." Hospitalizing an adequately treated child removes the child from the threatening home environment. Leaving

such a home environment, the child suffers a "rejection" psychodynamically, but, in spite of this rejection, the child becomes asthma free, often enroute to the Home, or within a week. Visits by the parents may cause a recurrence as late as one year after admission. And, in an occasional instance, because of some slip-up in staff personnel, a child may revert to intractable asthma and may have to be "parentectomized" from the Home itself.

It must be conceded that the psychogenic disturbance in this group of children with intractable asthma appears to be severe enough to interfere with recovery while they are with their families regardless of the duration and adequacy of the treatment.

The question arises as to what is this profound psychological disturbance and how does it operate to cause these children to react negatively to specific allergy treatment? Perhaps the metabolism of the cells of the body is badly disorganized and causes a profound physico-chemical imbalance with inhibition of immune response. This postulate would apply to children under specific allergy treatment which, from the beginning, was ineffective. It would also apply to a second group of children whose asthma was controlled by specific allergic treatment but in whom several or more years later, despite continued treatment, intractable asthma occurred. However, in this group of children it would seem that antigenic treatment has literally cured the child of asthma. However, when a profound psychological disturbance comes into operation, hostile forces may turn inward to seek an outlet through the previously-conditioned bronchi. It is not surprising, under these circumstances, that the mind recalls the old affliction, asthma.

Here the psychological disturbance plays a major etiologic role. This explains more easily why an appreciable number of children at the Home are free from pollen asthma without specific treatment.

Additional theories may be listed but the true solution to these locked secrets may be uncovered through basic research. Many scientific disciplines will have to be employed and integrated.

This challenge we accept. In fact, it led to the next stage in the development of the Rehabilitation Program. An interim research program has been initiated. The long-term research project involves building a special institute, since incorporated in this state as "The Children's Asthma Research Institute and Hospital" which we hope to have constructed and functioning several years hence. It is easy to predict that it will not only be an outstanding research allergy center but that it also will be the only institute of its type.

### INTEGRATED THERAPY AT THE INSTITUTIONAL LEVEL

DR. TUFT: I will present what we consider the integrated therapeutic approach at the Home. First, is parentectomy or separation from the parents. Perhaps as we discuss these topics with lay people we should not over-emphasize the word "parentectomy." We often use the word "separation." Here within our professional group we often speak in terms of the "bloodless operation" which is responsible for the immediate improvement of a number of these children.

When children come here three important elements play a role in their management: (1) group living, (2) allergy therapy, and (3) psychotherapy.

It has become an axiom in child care in this country that rehabilitation

from any chronic disease proceeds with greater dispatch in an environment solely dedicated to that disease. I refer specifically to bulbar poliomyelitis as an example. In the general poliomyelitis treatment centers, the patients with bulbar paralyses do not respond as well as they do at centers specifically designed for them. And, through the efforts of this Home, the rehabilitation of children with chronic intractable asthma proceeds better in this institution than elsewhere.

Children with a common ailment who live together seem unable successfully to impress each other with the severity of their illness. There is no harrowing tale one child can tell that another child cannot top as to the number of hospitalizations, the severity of the disease, how many times he had to return home from school, et cetera. As a result of our treatment program, our children soon learn to brag about good health rather than ill health.

The children are grouped according to age, sex, achievement and schooling. Our integrated recreation program is an important part of the treatment. Many of these children have forgotten how to run and play. They have been confined for long hours, many days and sometimes for months. When they arrive at the Home they see the only football team in the country made up of asthmatic players. They want to participate. We also have the only baseball team in the country composed of asthmatic children. In addition there are sports, one of which is boxing. There are arts and crafts as well as instruction in music.

In connection with specific allergy management, we have recognized that some of these children present active allergic disorders which continue to manifest themselves while at the Home. For example, fish ingestion can cause urticaria and pollen inhalation can cause hay fever or asthma.

A substantial number of children lose their asthma soon after arrival only to have difficulty later during the pollen seasons. They are given treatment with pollen extract.

As far as psychotherapy in treatment is concerned, we have a department headed by Dr. Stephanie Young, a specialist in the psychiatry of children. She has, under her direction, a group of clinical psychologists. This group provides play and interview therapy.

To better understand our program it is important to visit each of the buildings. As you inspect the thirteen buildings of the Home, you will appreciate the excellent physical facilities.

(Dr. Tuft introduced the three tour guides: Mr. Israel Friedman, the Executive Director; Mr. Jack Gershtenson, the Administrator; and Mr. Jack Frank, Public Relations. Prior to the tour a group picture of the Seminar was taken in front of the Simon Building and the children gave an excellent exhibition of Indian dancing.)

DR. TUFT: I think we can start the discussion with questions.

DR. HOMER E. PRINCE: How many children are there in the Home? How do you select them?

DR. TUFT: There are 150 children. Now I will defer describing the method of selection until tomorrow if you don't mind.

DR. PRINCE: Will you give a definition of "intractable asthma?"

DR. TUFT: Webster's New International Dictionary states, "not easily governed, managed or directed; indisposed to be taught, disciplined, or tamed; violent, stubborn, obstinate; refractory; not easily manipulated,

wrought, controlled or cured." If we think about it, we might see that most cases of asthma are easily managed, controlled or directed; and therefore you must assume that the small group of patients with asthma which does not respond to treatment is intractable. We define intractable asthma as severe asthma which requires frequent hospitalizations, and is essentially unresponsive to accepted therapy including adequate allergic management. This implies that the child has received hyposensitization therapy based upon a reasonably complete allergy study. Frequency of hospitalization depends on the available facilities and is therefore not uniform throughout the country.

Children with asthma who need continuous steroid therapy are considered to be intractable in the absence of symptoms because they are, in essence, masked chronic asthmatic patients.

DR. ETHAN ALLAN BROWN: This morning I believe you said that the average period of residence per child was eighteen to twenty-four months. What is the shortest and the longest time?

DR. TUFT: The duration of time is considered flexible. According to Dr. Peshkin's studies, children whose treatment lasted at least eighteen months but not more than twenty-four months did best.

DR. LAWRENCE J. HALPIN: I noticed one of the medications in the hospital is chlorpromazine. What are its indications?

DR. TUFT: May I defer discussion of your question? Before discussing specific treatments I think my topic "Special Experiences in the Management of Children at the Home," will clarify some of your questions before we begin a general discussion of specific therapy.

It is difficult to abstract two and one-half years of experience with this special group of children. Each day poses special problems. These may or may not be repeated, but nevertheless they concern management both from the medical point of view and from the complete consideration of the child. Therefore, I wish to select certain topics which I think will interest you.

To begin with, statistically speaking, how does "parentectomy" affect asthma? More than 500 children between the ages of five and sixteen have been admitted since the program was initiated. Fifty per cent of these children became free of asthma within a few days of admission and remained asthma-free during their stay. In 30 per cent, progressive lessening of asthma was noted during the first year with freedom from asthma during the second year of residence. In 10 per cent, the children were asthma-free upon admission, but relapsed during the pollen and mold seasons. In 5 per cent of the patients, the asthma remained unchanged, but did not interfere with many of the children's activities. The remaining 5 per cent continued to suffer from asthma, unrelieved by the institutionalization. Three children of this group died. These will be the subject of a special report.

I sometimes have to use restraint not to use the word "remarkable" when, after the child goes home, I report to the referring physician. There is no question in our minds that the transformation in these children who have suffered severe intractable asthma is amazing. Especially when we have had parents tell us that the child has never, previously for two or three years before admission, had a night free from asthma.

The parentectomy does work! And for the benefit of those physicians

whose cases do not fall into this group, let me also say it often works in those patients who are not now intractable but are nearly so.

The routine management of these children from the time they leave their homes is as follows: The children travel by plane. Until 1951 they traveled by train; the advantage of time difference is obvious. The children travel alone. Farewells are better completed at the home airport.

By the time the child arrives in Denver his asthma may have improved. He may be homesick. In a small percentage of the children homesickness lasts for several weeks.

At the airport the child is greeted by one of our staff. Independence is emphasized from the first moment. By that I mean the child is told firmly but kindly, "There is your bag. Pick it up and carry it. This is what you will be expected to do at the Home." There is often a greeting party for the new arrival, given him by the children in the building to which he has been assigned on the basis of age, sex and other obvious considerations.

After the physical examination has been done, the child is assigned to a counsellor. That is, either a psychiatric social worker or a clinical psychologist. Some of the counsellors are candidates for doctorates in psychology. The Counsellor sees the child immediately upon arrival and attempts through interviews to alleviate any homesickness.

In recent years the program of psychological testing has been implemented. The tests include the Wechsler-Intelligence Scale for children below the age of twelve. For children more than twelve years of age we use the Wechsler-Bellevue Form 1. For all children projective testing consisting of the Rorschach, Thematic Apperception, Bender-Gestalt, and Machover techniques is available.

Many of the children have missed a great deal of school. Their scholastic records, for the two or three years prior to admission, may have been poor. Their intelligence may be superior or within normal ranges. As the children improve we attempt to adapt them to normal programs of school studies. Tutors are available as needed.

The approach to the medical management of a case is predicated in some respects by the history. If the children have been on steroid medication, and today almost every one has been, we continue steroid therapy or gradually withdraw it.

When indicated, any general and specific allergy treatments are utilized.

The hospital is organized for the treatment of ambulatory and hospitalized patients. The nursing staff is on duty twenty-four hours a day.

We use nebulization solutions of epinephrine or its derivatives. A physical therapist determines the vital capacity and trains every child in breathing exercises. The breathing exercises are supplemented in group classes held in the evening. Twice weekly those in charge of athletics visit each building to help direct the breathing exercises.

A mild attack of asthma can often be controlled by breathing exercises alone. With nebulization we can control all but the most severe asthma.

If the asthma does not respond to nebulization we use epinephrine by injection or solutions of aminophylline given rectally. We do not use aminophylline in suppository form.

You are so familiar with the other medications used for the control of asthma that we need not list them.

The management of allergic manifestations at the home is comparable to their management elsewhere. All patients are tested by the scratch and intradermal techniques on arrival, before departure and when indicated.

Certain foods are routinely eliminated; for example, nuts. However,

most children are given an average diet despite the presence of positive skin tests to egg, milk and other foods. If urticaria develops after the ingestion of any food, that food is restricted or eliminated from the diet.

Many children are food fadists. I am afraid that we, as allergists, are responsible for such food fads. The children are afraid to eat certain foods long after the need for their elimination is over. Some of the children present problems in diet. We, however, encourage them to eat the questionable foods. Usually, when the child insists milk or egg cause urticaria or asthma, we use the "blindfold capsule feeding technique" and point out to the child, "Here, you took the egg and it didn't bother you. How can you explain not eating it in the dining room?" Often we are able to persuade that child to eat the general diet.

All allergy precautions are taken as regards bedding, furniture and floors.

It is interesting that in most cases the dust of the wrestling mats or the dust in the band room does not produce wheezing. During the first year no specific pollen and mold injections are given. Fully half of the patients who arrive at the Home with strong pollen skin reactions present no symptoms during the pollen season. Before arriving at the Home many of the children had long periods of treatment. Perhaps pollen therapy, as Dr. Peshkin reported, has really controlled the pollen allergy. The symptoms which were present at their own homes during the ragweed pollen season were symptoms not only of ragweed pollen sensitivity but also of a psychological nature.

The pollens here include Eastern pollens. In addition, we have the Chenopod group. Some of these children acquire Chenopod sensitivity and take treatment while at the Home.

Mold sensitivity is important in this part of the country. A north wind prevails during the winter and a south wind during the spring, summer and fall months with very few winds from the mountains. Our weather is determined by cold fronts which extend from the North, meeting warm fronts moving north from the Gulf. The mountains block much of the Pacific weather so what we get here is dust blown in from the South and North. Occasionally during the spring there are east winds from the plains. During a dust storm many of these children with asthma are entirely free from symptoms. Their threshold under our special living conditions must be very high indeed.

Our experience with upper respiratory infections at the Home is rather unusual. Ninety-five per cent of the infections are not accompanied by asthma in children with an admission diagnosis of "infectious asthma."

Additional data are available on the role that emotions play in children with intractable asthma admitted from the local area. The records show that twenty-four children from the Rocky Mountain area and seven children from Denver and its environs have done as well as comparable groups from more remote places. Separation, or "parentectomy," although it is from around the corner to this institution, is a significant factor in the rehabilitation of these children.

Some children who present symptoms of pollen allergy during the first pollen season here are subsequently treated immunologically for the second pollen season and usually respond well. This leads us to believe that emotional overload does affect immunological mechanisms.

Juvenile delinquency is an important problem. Some children who lose their asthma and to all intents and purposes become delinquent or very dif-

ficult to manage within this environment. There is a substitution as it were, of the delinquency for asthma. The question is, which is preferable? I suppose we would rather have the delinquency than the bronchospasm. However, it is difficult to control these children in an environment organized for the treatment of chronic asthmatic patients.

If a child in the Home tries to get out by acting out his problems, we must often return him to his own home. There is nothing we can do about it. Some day the Home hopes to acquire special personnel to handle these children.

As far as we are able to determine, the incidence of broken homes from divorce, death, et cetera, is no different for the nondelinquent children than it is for an average population.

DR. PRINCE: You mentioned that you test your newly arrived children. Do you test them for the allergens in this environment or for the allergens to which they were exposed in their previous environment?

DR. TUFT: We attempt to do both. In those who arrive from the East, and not from Texas, the allergens are tree, grass and ragweed pollens and molds.

DR. SAMUEL ROSS: How do your tests compare with those reported to you from the referring physician? To what extent is there agreement?

DR. TUFT: I must say that that depends upon who did the tests. The tests that would come from a group equal to this often agree with those that we get.

DR. ROSS: What type of allergens do you use when you test for foods and inhalants? Do you prepare them yourself?

DR. TUFT: No. They are purchased.

QUESTION: Would you have time to demonstrate the breathing exercises?

DR. TUFT: Not at this time, but mimeographed copies of the instructions will be given you. May I say that these were taken from the British Manual, although modified for children, and also from the Fein and Cox paper which I believe appeared in the ANNALS OF ALLERGY. (See Fein, Bernard T., and Cox, Eugenia P.: The Technique of Respiratory and Physical Exercise in the Treatment of Bronchial Asthma. 13:377 (July-August) 1955).

### SPECIAL EXPERIENCES IN INSTITUTIONAL MANAGEMENT

QUESTION: Why do you use nebulization treatment first rather than the injection of such drugs as epinephrine?

DR. TUFT: There are two reasons. First, many of the children have suffered too many injections. Second, nebulization treatment gives them a sense of doing something for themselves rather than of someone else doing something for them. If nebulization is properly used no great problems arise. The chest physicians use nebulization treatment more, I think, than we do. Perhaps you have some criticism of the procedure, but we find that it works as well as does the subcutaneous injection of epinephrine. Psychologically, it seems to be better for the children if when they go home, asthma occurs. A nebulizer is a reminder that "here is something

I can do for myself." The general idea is to try to get these children out of the habit of depending upon others for treatment and to prevent the parents from becoming overconcerned. This is really a part of the process of "parentectomy."

DR. HALPIN: Can you answer my question regarding Compazine®?

DR. TUFT: When Thorazine® was issued we used it in children with behavior problems on the basis that anxiety went along with asthma. We hoped to avoid that asthma solely or chiefly due to anxiety. Thorazine did not help these patients. We also used other tranquilizing agents and none of them seemed to work well. At the moment we prescribe Compazine for a number of children to learn whether there is direct action on the asthma. At this moment it seems there is no direct action because many of these children have taken Thorazine without any help or effect. We have one patient who came to the dispensary every day or every other day with mild wheezing, easily controllable but, present every day, and particularly on Monday before school. This child has been completely controlled on Compazine and I cannot tell you why.

DR. HALPIN: What is the dose given?

DR. TUFT: 15 to 20 mg daily.

DR. GEORGE BLUMSTEIN: I have several questions about infection and asthma. Do you imply specifically that the patient who has overcome his asthma here is not bothered by infection, or was yours a general statement that none of the children are bothered by infection?

DR. TUFT: I did not mean that. Severe infections occur in approximately the same number and degree or perhaps to a greater degree than in another environment for only one reason. The children live together. If an infection starts in one building, it may spread through all of the Institution.

DR. BLUMSTEIN: What is the effect on the asthma? Are the children actively asthmatic at the time that they are infected?

DR. TUFT: No. What I was trying to indicate was this. The child comes in, loses his asthma, and develops an infection and there will be no asthma in 95 per cent of the cases.

DR. BLUMSTEIN: What about those who continue to be asthmatic?

DR. TUFT: The infection may sometimes aggravate the asthma. The patient you saw in the hospital today is an example.

QUESTION: Are these the patients for whom you prescribe steroids?

DR. TUFT: Yes.

QUESTION: Do you prescribe antibiotic agents with the steroids?

DR. TUFT: Yes. Some patients begin with antibiotic drugs and then take the steroid.

QUESTION: What is the proportion of asthmatic patients in the infirmary during the winter as compared to the summer?

DR. TUFT: The same group of chronic severe asthmatic patients is in and out of the infirmary summer or winter. That doesn't change, but we

do get a new group coming during the summer when symptoms caused by the pollens and molds are added to what the children usually suffer.

QUESTION: But you do have one group during the winter and another during the summer?

DR. TUFT: No. The summer group is added to the year-round group. In other words, there is one group intermittently hospitalized throughout the year. There is another group during the summer pollen and mold seasons. The pollen and mold group is small.

DR. BROWN: Omitting discussion of the asthma for a moment, since this is a home for asthmatic children, what about nasal problems?

DR. TUFT: I expected that question. I suppose we have neglected the nasal problem. We are so concerned with asthma that we don't bother much with nasal problems, excepting when they become troublesome.

DR. BROWN: I worded my question incorrectly. What I meant is, do the children with nasal problems, such as hay fever, improve as the asthma improves? So many of our asthmatic children present as well, eczema and hay fever.

DR. TUFT: Some nasal symptoms get worse and some improve along with the asthma. It is not dependent upon pollen sensitivity alone. We have seen several startling results in atopic dermatitis. We have also had startling reversals. The asthma disappears but the eczema grows worse. The usual picture is that seen in your own practice. There was one patient in whom the eczema disappeared and then recurred when the mother came on an unscheduled visit. The eczema did not subside for about three months. The patient is at home and as far as I know she is now free from eczema and has been for six months.

QUESTION: What is the influence of humidity on the absorption of the pollen and other allergens, in comparison with their own home environment? The humidity in Denver is so low.

DR. TUFT: Allergists in practice here feel that pollenosis, uncomplicated pollenosis, can sometimes be more severe than it is in a humidity-laden area. We discussed this at the Rocky Mountain Allergy Society. It was generally conceded that dry pollen seems to intensify the allergic response.

DR. NORMAN W. CLEIN: You said you used nebulizers twice a day?

DR. TUFT: Yes.

DR. CLEIN: Why not use epinephrine 1:100 solution and compare it to whatever you are using?

DR. TUFT: We tried epinephrine 1:100. The children complained. They sometimes grew a little pale and in some of them the rapid heart action made them afraid. We discontinued its use.

DR. HAROLD A. ABRAMSON: I have used epinephrine 1:100 for twenty years. It is most satisfactory.

DR. CLEIN: I want to say that for twenty years I have also had all asthmatic children use a nebulizer with 1:100 epinephrine. I have used the one recommended by Dr. Metzger of San Francisco. I have yet to see a child bothered in any way. When I read papers by physicians who

condemn nebulizers I wonder whether they have used them and over a suitable period of time. I see you have used nebulizers here a great deal with evidently no trouble. You have been using them on the worst cases. Certainly you should find trouble here if anywhere.

DR. TUFT: Yes. I would like to close by saying that the pediatricians here believe very much in "cold mists" in treatment of asthma. We do use cold mists in some of these patients. The humidity is usually very low here and we think the bronchial secretions may be thicker and as well, difficult to raise.

We have associated with us, a psychiatrist who has devoted all of her time and training to children. Her topic will be, "Observations on the Psychiatric Aspects of the Intractable Asthmatic Child in the Institution." Dr. Stephanie Young of Denver.

### PSYCHIATRIC ASPECTS AT THE INSTITUTIONAL LEVEL

DR. YOUNG: In this Institution we have an opportunity to observe the emotional problems of the intractable asthmatic child. The variety of problems is great. Each child has different past experiences, some of which help to aggravate asthma, such as parental overindulgence and overprotection, divorce, economic deprivation, emotional illness in the parents, and others. In spite of these variations, I am impressed by two characteristics seen in many children, a pronounced tendency to avoid anxiety and as well, a tendency to control other people. While these tendencies do not give a full picture of all the various little personalities we have here, I feel that they are so often seen and also so markedly changed during the child's stay here, that they deserve some attention.

In reading the children's histories I try to imagine how these tendencies develop. Many of you probably better observe the asthmatic child within his family group and I hope that you may correct me. It seems that in most families the anxieties aroused by the onset of the asthma lead easily to a certain reaction to anxiety, that of avoidance. Because avoidance has played a role in medical management the illness often extends beyond the necessary medical reasons to a pattern of avoiding school, group play, hardships of weather and exercise. A small child going through this experience can easily get the impression that anxiety can be overcome only through avoiding danger. In contrast, the healthy child would accumulate experiences of mastery as he is more often exposed to hardship.

The pattern of avoidance leaves the asthmatic children with a false sense of security which can easily change into anxiety. Having a few experiences of victory and mastery the child turns to another anxiety defense, namely controlling people. Histories show attempts by children to control parents and if unsuccessful, asthma would recur. A tendency to control is often seen in the children at this Home, particularly in new patients. For example, a ten year old boy demanded daily telephone calls to his parents during the first month of his stay. He spoke to me during several interviews worrying that something had happened to his mother; fears that he might stay here too long, and that he would not be able to convince his parents that his asthma had improved. He was beset by many anxieties and broke into tears and yelled for nearly an hour because he wished to make another telephone call, of which he had made many. His fearfulness and apprehension were discussed with him and after four weeks he began to smile about it himself and no longer at-

tempted to control people. He admitted telling horror stories about the Home to his parents. Then he found they became frightened; which in turn, frightened him. By the time he could explain all of this, he could also laugh about it.

This episode may exemplify what is involved in the frequently described "controlling behavior," the anxiety and helplessness from which the child desperately seeks relief by controlling his environment. As the child becomes more controlling of others he finds it more difficult to solve his own problems. It also amplifies the role of the psychiatric interviews and counselling in the treatment of the children. Every effort is made to help the children verbalize and stand up to their fears and anxieties.

Many anxieties arise in the process of growing up, as for instance, learning to be less impulsive, and getting pleasure in socially accepted ways. Many of these anxieties are unconscious. The children feel an unknown sense of apprehension and some of them try to explain this in terms of fear of dogs, cats, weeds, taxicabs, crowds, and so on. We often hear about these fears in the beginning. They are actually long-standing anxieties about difficult life situations for a child, such as the arrival of a new baby, entering school, conflict about loyalty to either parent.

I believe that the asthmatic child is more prone to anxiety and develops more of it quantitatively than do others. Coinciding with some of these average events in the home, there is often a history that the asthma became more frequent. This results in staying closer to the mother and further conflicts come from that situation because the child can become very babyish and that in itself brings the danger of disapproval.

The emotional overload appears to be an accumulation of anxieties and past experiences of helplessness. Then comes the emotional re-orientation when the trip to Denver is considered. The child is trusted to undertake something as dangerous as a long trip alone. When we see him after arrival he may have been fearful about the trip but usually he is proud. He has gained pride and some feeling of strength. Now he is exposed to a group of other children. This, too, presents a new and frightening experience to most children since they have been in many instances staying away from groups. Their fear may be expressed in crying, in wishing to go home, in tantrums, or asthma. Some avoid any close relationship within the group.

In counselling, in psychiatric interviews with the children, they are helped to express fears which prevent them from making close relationships with their companions. The majority of the new children need this help, and through playing and talking the child begins to face some of his conflicts and no longer avoids them. Meanwhile, other things have happened to alter this avoidance pattern. He has joined in games, physical activities, in eating almost everything, in going to a new school, entering into a new form of living, in sharing with other children, all this through the patient guidance of the houseparents. The child begins to feel a sense of pride and accomplishment in doing things he originally feared. But some anxiety persists. The child feels more confident about overcoming these anxieties. For instance, one ten-year-old girl spoke to our counsellor of fears of returning home. She then added, "But I was just as afraid when I came here of the new children and new school and I learned not to be, so it may be the same when I go home."

The emotional overload of fear is reduced. A nine-year-old boy said, in effect, "When I left home I used to be stingy. What helped me most

here was to learn not to be." He was jealous of sharing his mother with anyone, that is his baby sister, father, or guests. These feelings were associated with anxiety and contributed to his frequent asthma. Here he found that he could share and have fun in group relationships. He was much more confident about his return home.

A girl of similar age was also anxious of leaving. She had fears about loyalty to her parents. She particularly indicated that she wanted to be independent of her mother. She expressed this in a fantasy of wanting to be an Indian. She then would be able to use sign language and would not need to talk and confide in me or any other women. As an Indian, she would be able to find her own food in the woods and would not be forced to ask anyone for help. Following this fantasy the child became anxious during her next interview and expecting me, perhaps, to be critical. She began to breathe rapidly. After we discussed her fears the breathing subsided. This child was rebellious during the day and during the evening, hyperventilated. The psychiatric studies were not completed, and it was recommended that she and her parents seek child guidance together in their own community.

A fourteen-year-old girl was much more anxious about loyalties divided between her divorced parents. Her anxiety about dividing her loyalty became acute whenever she tried to make more than one relationship here with various grownups. During the interview she immediately burst into tears for fear of losing her counsellor if she came to see me. Her anxiety was so great that one expected all kinds of catastrophes. She thought one could not be sure about psychiatrists: they could make a patient feel worse and take all his money. She thought we would spread rumors about her, and that I had my window open so people could listen in. As we discussed her fearful expectations, she gradually became more reasonable. When she ended the interview she said she had learned here not to be afraid of her asthma and hoped to become less afraid of her difficult situation. For a year this child was seen regularly for interview by her counsellor, and as do all other children, received guidance and tolerance from her houseparents and our medical staff. She has changed from a baby to a strong girl, to an outgoing young lady. She is particularly eager to work and become more independent. She is interested in being glamorous and in joining social activities. Although not entirely free of anxiety, she is much more hopeful and courageous.

Other children tackle the process of becoming courageous through anti-social behavior. Mild group epidemics of stealing or destructiveness may occur. This requires patience and freedom from anxiety on the part of all the staff until skillful handling can direct courage into the right channels.

While the counselling and psychiatric interviews provide help with anxieties, contact with all other members of the staff and group experience offer equally as much support for the child. Children as a group generally discourage baby behavior, irresponsibility and selfishness. At the same time the group offers a child channels in which he can express his impulses. For example, a group of small girls played for weeks with their dolls and acted out a home situation. Some children played out wishes to be babies and achieved satisfaction by this socially-accepted method. Others could express resentment by taking it out on the dolls. Playing together helped them all feel less anxious. They were sharing the load of anxiety and making it lighter. Thus, they had their own play therapy.

They played out the fear of a "small" patient in relation to a "large" doctor. In their play they were doctors and no longer helpless. This helped to overcome feelings of helplessness. Their play also led to an investigation of their anatomy through the anatomy of the dolls because some children were anxious about being curious of sex. This experience diminished anxiety. The housemother gently guided the play, directed the girls to play and practice cooking and sewing and taught them to postpone and channel their impulses.

Many children can benefit from group experiences and common sense guidance by the houseparent. Those who do not enter into relationships at least feel comfortable. However, there is a small percentage of children, perhaps one per cent, whose fear of other children increases during their stay. They become panicky and unable to recognize reality. They see other children as monsters who want to torture them. They feel they may be spied on through windows by unknown people; that their food is poisoned and mixed with broken glass, and fear other catastrophes. Naturally these children are emotionally sick but, not incurable.

Some years ago we were so alarmed by a psychotic episode in a ten year old boy that we sent him home immediately for further psychiatric care. Since then we have become more courageous. A girl who remained mute, suspicious, and refused most of our food for weeks was helped to return to the group. Patient nursing and feeding in the hospital, and loving care by the housemother who permitted the child to remain at her side until the fears subsided, helped most.

Other children, who were similarly disturbed, presented particular problems in terms of being destructive, attacking, and presenting severe tantrums. I believe that in each of these cases, the parents had really been in search of institutional treatment to solve the child's emotional problems. Actually the search for institutions which offer treatment to the psychotic child is a difficult one. There are only a few psychiatric institutions for children. Most of them are expensive because they have as many skilled personnel as there are children and also because a good deal of destruction is encountered. We find it almost impossible to find further institutional treatment for disturbed children. For this reason I am particularly happy and proud of our staff personnel who go out of their way to help the children who need psychiatric institutional treatment so badly.

DR. TUFT: You have heard a masterful presentation of the psychiatric aspects of the institutional care of these children. We would like now to relate this to private practice. Dr. Harold A. Abramson.

### PSYCHIATRIC PROBLEMS IN PRIVATE PRACTICE

DR. ABRAMSON: Mr. Chairman and Members of the Group: I thought it best to describe a scheme which I find useful in discussing the psychosomatic management of any chronically-ill person. I speak of the Psychosomatic Pentagon.

The base of the pentagon is the laboratory. In this case it represents skin tests, of course, and other laboratory procedures. On one side is the patient, here a child. On another side are the parents (the houseparents in the Home), the siblings and teachers. Another side represents the doctor or doctors and the consultants who are in the background. We have this complication because one doctor reacts with another doctor, and finally (on the left side of the pentagon), we have the symptom—asthma and other forms of allergy.

Now of course this is only a scheme, but what does it mean? It means that in approaching the total treatment of the chronically-ill asthmatic or emphysematous child we have a whole series of phenomena which we must treat simultaneously. We cannot treat the asthma alone. We cannot treat the parents alone. The doctor cannot relieve his own anxiety by using a nebulizer or not using one. I think two of you gentlemen disagreed about nebulized medications.

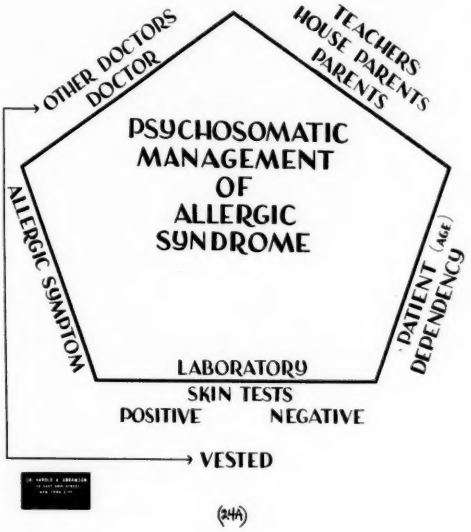


Fig. 1.

Each one of these components enters into a network involving the whole treatment program. When we compare this general outline which I have used in private practice with the outline of this network of transactions or interaction as it is employed in the institutionalization of the child, certainly things become important in terms of comparing private practice with what I understand to be going on in this unique institution.

I think that both in private practice and in the Home we should continue to use available laboratory procedures. I have found less flexibility in private practice than we have here in the Home. In private practice I have found that the parents have a vested interest. The word "vested" is placed on the chart, to explain on a strictly physical basis, the child's intractable asthma. There is always a search for a purely physical cause, for an allergen, for some underlying things that we have missed that might be causing allergic symptoms. Here in the Home the vested interest of the parents or of the doctor in the home community who may not wish to go into the psychological aspect does not apply. Here in the Home there is greater freedom of expression of the Staff. The child comes to the Home with certain feelings every child needs and has. These needs are retained into adult life, but are transformed into mature relationships. We call them dependency needs. Now these dependency needs of the child,

the need to be taken care of and to be loved, are suddenly interrupted by removing the child from his own home. This is complicated because the child's needs are not only felt toward parents and siblings but also toward his doctor and teachers; in fact with the whole cultural pattern in which the child moves. Furthermore, a special problem arises when the child enters the Home. The dependency needs in the chronically-ill allergic child in my experience are special and unique with one or the other of the parents. Broadly speaking, especially in cases where eczema is present, there is a special relationship with the parent of the same sex in children about eight or nine or older. In younger children I am not so certain. So, the relationships with the parents may be specialized, and removing that child from a particular parent may introduce another complication. When the child is brought to the Home the burden of satisfying these complicated dependency patterns is thrown upon the Staff.

Now let us transform our Psychosomatic Pentagon to the Home and show some of the changes which occur. We no longer have parents, but we have Houseparents. We have doctors but the doctors are no longer concerned about the parents' attitude, in the same way as in private practice. It is with great trepidation that I say to the average parents who bring their child in, "Do you think that your child is worried about something?" Here this does not occur. We have houseparents and doctors and teachers here. This setting imposes a tremendous psychological force on the child. It is like somebody going into the Army and losing his asthma or someone going into the Navy and losing his eczema, or someone going on a threatening mission and losing his allergy.

This Institution not only has houseparents but it also has a Psychiatric Staff which now has the job of meeting the dependency needs of the child. In other words, the Psychiatric Staff Members in this Institution are the new parents. This is named the Counselling Staff. Let us call it the Psychological Staff.

Now, special problems arise. How do you treat the little girl who gets on your lap and wants you to hug and kiss her the way she wanted her father to? She may not have done it with her father. These are unique problems that have not been worked out but the Staff is deeply concerned with satisfying the dependency needs which parents or the siblings would ordinarily meet.

One of the important points brought up by Dr. Young concerned the child who comes into the Institution and who has previously avoided his anxiety by avoiding school, play, group hardships and exercise. I believe in the use of anything that will help a child to function in a normal fashion physically. I do not hesitate to use a nebulizer three times a day if it will work. I always reply to parents, who say, "Well, the child will get dependent on the nebulizer"; "It's much better to have that child play football and use the nebulizer than not to play football and not use the nebulizer." I have boys on high school football teams with a nebulizer in their locker rooms. They use the nebulizer, take an ephedrine capsule and go out and play football.

I agree with Dr. Young that every effort should be made by the doctor in private practice to prevent the avoidance type of treatment of the child's anxiety. It really is not the child's anxiety alone; it is the parents' anxiety very often or else the doctor's anxiety. I advise girls to take their nebulizers to dances. I have patients with oxygen tanks at home taking epinephrine 1:1000 for fifteen minutes three to four times a day,

with no damage whatsoever. It does no harm when used properly. It is not enough to give the patient a nebulizer and an oxygen tent and say, "Use it." The patient must know how to use the nebulizer properly as well as to be skilled in the breathing exercises. There are many tricks in the proper use of nebulizers.

I agree with Dr. Young that group play, school hardships and exercise are important factors here. Dr. Peshkin and I know that patients we studied together in research programs can ski away from home without asthma but have severe asthma at home. We see all symptoms disappear when men leave their wives and children and go skiing in all kinds of weather. These are allergic people; these are pollen-sensitive people.

I think one of the Institution's benefits to children is that every effort is made to help each child verbalize, to say what is on his mind. I ask parents to do this always. One parent asked me "If my child says, 'I hate you,' what should I do?" This parent was astonished when I said, "Pick him up and say, 'I love *you*'." The parent said, "You don't think he should be punished?" I said, "No. If the child says, 'I hate you,' it means that he trusts you enough to verbalize the anger he may have at that time." Perhaps not all psychiatrists would agree with me, but it works with these children. I had one child call his mother a five letter word for three years before the asthma disappeared.

Dr. Young has pointed out that there are epidemics of stealing. A certain symbiotic relationship is evident. The children are able to form gangs without fear of reprisal. This cannot be done in the home. The children in a family cannot readily get together and attack the parents. In the Institution this is possible. Here sibling rivalry is easily replaced by sibling symbiosis. The children can form units. They can get together with children with the same attitudes and defy the Institution. They can express anxieties and hostilities much more than they can in their parents' homes. It is the job of the physician at home to explain to parents how important it is for children to verbalize their hostilities. Now, what do I do in private practice? I always recommend that the parents read English and Pearson's "Emotional Problems of Living," and I go through it with them if they are willing to learn something about the psycho-sexual development of the child. The Institution here does not have that advantage.

DR. PESHKIN: I recommend another fine publication, "The Patient Speaks," by Abramson.

DR. ABRAMSON: I have some other matters that I would like to take up with you. I feel that the football and baseball teams are models of what should be done in private practice. In such we cannot say to the parents, "Your child is going to get intensive treatment for two years." Parents are resentful and suspicious of prolonged therapy. They always want to know how long it will take. We have to "sell" the parents. Here, as Dr. Young pointed out, many parents are glad to have their children come. They are happy in many cases, to have their children come here to solve not the children's problem but the parents' problem. This is an important aspect of the over-all problem.

There is one important difference in institutional care not found in the home. This Home is a unique center dedicated to the maintenance of the parents' comfort and the maintenance as far as possible, of the family unity. In other words, the home in general, even though it might like to

have a sick child around for some psychological reason of its own, is hostile to the disease and the child is in a definitely hostile, anxiety-producing environment. This Institution is very different indeed. We cannot emphasize that enough. It is important for us in private practice to reorient parents on how to handle their own hostility toward their asthmatic child.

Here in the Home psychotherapy is routine. As I above mentioned, there is no problem here. In private practice I feel that it is the parents who have to become oriented primarily rather than the child. The child may be given some form of psychotherapy. Some of the things I use may be of interest. For example, watch the child draw. I do not mean interpretation of drawings, but just spending five minutes with the child and letting him draw and talk about his drawing is psychotherapy. Or watch him play or let him use the tape recorder or ask him about school. All of these institute new relationships for the child and are the beginning of psychotherapy and assurance that the support of the physician is given him.

I would like to discuss the practical management of the parents (which is not done at the Home as yet) in terms of two theories: the Rejection Theory of Allergy and the Engulfment Theory. I think you have all heard and read the basic psychodynamic notion that the allergic child is consciously or unconsciously rejected by his parents and therefore, he is allergic. Of course I feel, as Dr. David Levy does, that all parents reject their children but that this rejection has little to do with the nature of the allergic process. I feel that more important is the fact that the parents try to have the children act out the parents' own life goals; that the parents do not wish the children to have lives of their own; that the parents keep their children in psychological chains and try to force them to live in a pattern which is related to the culture and upbringing of the parents. I do not believe that this is true specifically of any one segment of the population. I find the codified behavior attitudes of the parents are even greater in the upper social and economic classes than in the lower. The higher up one goes in the cultural scale and greater the number of taboos, the more strict the codification and the more the child must fit in with the family structure. So it is not the first generation group but the tenth generation group I think, that has the worst time of it. Royalty, for example, must intermarry with royalty. I think that if you will tell parents what I told another group today, "I know you love your child well enough to give your life for your child, but are you willing to let your child have a life of its own?" If you are willing to do that, willing to understand why the child needs to develop independently, then I think the allergy will become better slowly through the years.

Dr. Ross: I would like to say something about one thing that I found valuable in the management of the parents. I am referring to Dr. Abramson's exceptionally lucid article in *Parents' Magazine* appearing in 1953, September issue. The title of the article was, "If There is an Allergy in the Family," by H. A. Abramson and L. F. Connell. It covers the whole gamut of physical, psychological and social management in such a way that I have purchased hundreds of reprints and have given them to parents who bring their children to me. As a part of the education of the parents I can at least try to help them overcome some of their own hostility not only toward the child but also toward me. In that respect I have had good

results with what few patients I have been able to manage. I highly recommend that article.

DR. MAYER A. GREEN: I would like to ask about the reaction of abandonment, as experienced by the child who undergoes this separation from his home and how it affects his adaptation to his new environment and how it is correlated with the anxiety of nostalgia and also his dependency reaction as far as the Counselling Staff is concerned. In the same vein, consider the fact that a minor percentage of the patients require this rather drastic management. There has been little emphasis on this here. We are apt to get a narrow perspective. Certainly in my experience I never found it necessary to recommend this type of bloodless surgery and I don't know whether it is true of my area, but I have had the good fortune of being the Regional Consultant for twenty years and never have I had a case referred to me to pass upon his adaptability to the Home.

DR. ABRAMSON: I would like to take the latter part of your questions first. I have observed that "bloodless surgery" is often done by the family itself. Parentectomy is practiced within the family. Many of my patients are shipped off by their families to camp, to a grandmother, to an aunt out west! "Parentectomy" was discovered long before Dr. Peshkin emphasized it. Secondly, Dr. Tuft stated that asthma often is replaced by juvenile delinquency. Now, Dr. Peshkin does not mean that all intractable asthmatic children are going to be cured or treated satisfactorily by the present program. What he means is that there is a group among the intractable asthmatic children for whom the relationship with the parents is intolerable in terms of their asthma. It is a fact that the group is helped by leaving the parents. That is not theoretical! It is an empirical fact! The statement that the child becomes a delinquent here, should be viewed first in terms of private practice. Such a child usually has a symbiotic relationship with the parents that is not or has not been recognized. In these cases, both the parents and the child must be treated psychotherapeutically. For such children "parentectomy" in my opinion seems to be contra-indicated. The only thing to do, at present, is to make a test situation by sending the child to the Home.

Here the dependency needs have been satisfied and they are being satisfied more and more as the insight of the Psychology Staff and the other Staff of the Institution grows except for those children who are too strongly symbiotically attached to their parents. These may be the psychotic children. Dr. Young, couldn't that symbiotic relationship be transformed in the Home?

DR. YOUNG: That may be.

DR. ABRAMSON: I think that the parents and child have to be treated as a unit. Dr. Green, does that answer your question?

DR. GREEN: What about the reaction of abandonment as far as the child is concerned?

DR. ABRAMSON: The child comes to this Institution, to a set of house parents, to a whole series of new factors which almost say, "Look, you are the most important child in this country. You are going to be taken into this lovely place and every one of your needs is going to be satisfied. If you do not like this psychologist, you will have another. If you do

not like boxing gloves, you can play baseball. If you do not like fish, you can eat something else." The anxieties of these children are relieved. The children are not abandoned. They can not change their natural parents as readily as they can their house parents.

DR. TUFT: To re-enforce that point; we very rarely have difficulty with this reaction for any length of time and I tried to indicate, as I try to reassure myself all the time, that we are really not that important to our children and we had best leave them alone.

DR. GEORGE BLUMSTEIN: I feel that this is a form of expressive medicine that is being practiced more and more not by individuals, but by teams. The time is not far distant when many of the things being done outside the framework of the child's home will be done by teams inside the home on an ambulatory basis . Also, many of these problems depend upon the outlook of the physician in charge of treatment. We know that many of the ranking allergists of the past were immunologists who knew nothing of the psychological aspects of what is being discussed here today. At this point we are discussing a special and minute group of everything that we see. We who are conscious of the psychological factors involved probably do this every day in our offices. We are practicing a brand of psychiatry by no special name.

DR. TUFT: The number of children with intractable asthma may be small in your practices but if this only applies to one per cent of the childhood asthmatic patients in this country, the total number is about 25,000. That is a large number of patients not receiving treatment. This group of children should not be ignored.

DR. CLEIN: Some years ago I spoke at the Rocky Mountain Medical Conference on the subject of allergic problems. There was a physician from the University of Utah, the head of the Psychiatry Department. He talked on the psychological factors in allergy. The next day there was a headline in the newspaper, "Psychiatrist Says Allergy Is in the Mind; Child Specialist Says It's in the Blood." That summarized just what goes on. I wonder how we are going to present this to the public and the doctors to prevent the condition we find at the University Medical School at Seattle, the University of Washington, where the Psychiatry Department teaches that allergic problems are all psychological.

I want to tell a story to encourage you about your football team, which I understand hasn't won a game in four years. During World War II the Air Force Base in Spokane, Washington, had a baseball team and this team played a school team composed of young mentally retarded people. The aviators who were the picked men of our generation were beaten by the mental defectives. The point is that the mental defectives had been playing together for fifteen years. They won because of that.

### PARENTECTOMY—SUPPLEMENTAL CONSIDERATIONS

DR. PESHKIN: I would like to talk about two items, which I have kept in mind for years and that have not been covered. When all of my papers are published I think most of your questions will be answered. I envy the doctor who doesn't see an intractable asthmatic child. I see them. I am a specialist in my own failures as well as in those of others. These failures can hardly be accidental. There surely must be another reason—the emotional factors in chronic illness.

In 1926 Dr. Bela Schick, as director of the Pediatric Department of Mount Sinai Hospital in New York, encouraged the work covering the next four years. That study later formed the basis for the program here. Following review of this study, the role of environment and psychological forces took on a new meaning. Hospitalization necessitated the separation of the child from his parents. It was distressing to listen to a child scream pitifully and see it frantically clutch at its mother's dress. Following hospitalization you would expect a child to develop panic. However, the worst asthmatic and most badly behaved child soon settled down. We did not use the refined techniques for separation that we use today. We did not have today's knowledge of human behavior. In fact we did not know anything about psychology or of the handling of people. We literally ripped the mother and the child apart.

The facts were that when the children were in the ward for several days the asthma usually cleared. They adapted themselves well to the separation. Some of the children cried and whimpered for as long as three days. Why was there no asthma? The question baffled us. Why does the child cling to the mother so strongly when there was so much hostility? And if the child needs to hold on to his asthma, why does he strenuously resist separation from her? And with separation accomplished, why the clearing of the asthma independently of the presence or absence of the allergens?

One psychiatrist postulated, "The child unconsciously feels that separation from his mother would clear the asthma or that he would no longer have a need for asthma." Then the child is actually saying, "Don't you take me away from my mother. I need to punish her. I want to continue to punish her." That is one of the reasons why I maintain that a change of human environment, "parentectomy," is not usually one-way. It is mutual. Often the child punishes the mother much more than the loving and indulgent mother punishes the child, consciously or unconsciously. The process of separation has to be explored psychodynamically.

During World War II when I had to select children for the Home by application only, I recall there were two children and their hypomanic mother living in a most deplorable condition in a trailer camp in Tucson, Arizona. The children had intractable asthma. The family was abandoned by the father. The local social service agency appealed to us to admit the children. I was afraid to accept the children without a neuropsychiatric examination. The psychiatrist stated that while it was not the established practice to separate children from the home and it was generally a harmful procedure, nevertheless, the plight of these desperately asthmatic children was of immediate importance. It was concluded that separation from the mother to a warm emotional climate would be helpful and most likely free them from asthma.

I never forgot that experience. These children remained free from asthma during their residence in the Home without the need of any specific treatment for allergy.

Some concern was expressed about the effects of "abandonment" on the children sent to the Home. Abandonment should not be confused with "parentectomy." The latter involves the temporary separation of the child from his parents for the explicit purpose of getting it well. The child and the family are properly prepared for acceptance of separation. Abandonment is obviously another matter. As a consequence of the continual suffering from severe asthma (despite various treatments given by

many physicians) may not the child sense that it is being abandoned by the physicians by their failure to give relief or perhaps by their failure to prescribe "parentectomy" and the rehabilitation program that is available in an institution such as ours?

I believe, that psychiatrists, allergists and other physicians who are opposed to "parentectomy" for the intractable asthmatic child may one day acknowledge that their objections are neither valid nor realistic when the facts become known to them.

One of the obstacles to the development of the rehabilitation program and one which is not yet largely overcome, is the social worker of the old school. Our antagonists hold firmly to the concept not to separate a child, not even an intractable asthmatic child, from the family constellation.

In this connection, it is of interest to note that at one of the recent conferences on Childhood in Washington it was concluded that 10 per cent of delinquent children belong to a special group of "malignant" delinquents. These children were physically well. It was not possible to help this group of children with any form of treatment while they resided in their own homes. These children had to be separated from their families. It was only then that the children responded favorably to therapy.

Fundamentally, there is no essential difference in the initial approach to either the rehabilitation of the malignantly delinquent child or of the intractable asthmatic child whom we "parentectomize" to break the circle of persistent chronic illness. Once that circle has been broken the intractable phase of asthma is interrupted, so making it possbile for the child to respond to conventional treatment. The intractable asthmatic circle is not easily broken from a long range point of view. We have learned that "parentectomy" of six to twelve months (as compared to longer periods of time) is therapeutically less effective particularly with respect to recurrence of asthma and response to treatment after return of the children to their families.

Our immediate concern is not how many children have asthma but rather to explore the mechanism causing some of them to become intractable which if not controlled or cleared may prove fatal.

Some of my colleagues tell me, "I don't see intractable asthma." I then ask: "What do you call intractable asthma?" It has already been defined. Surely there must be a dividing zone between troublesome asthma which responds to treatment and intractable asthma which does not. When the diagnosis of intractable asthma is established by other physicians why do they feel that the child is in imminent danger? They are aware of the child's inability to respond successfully to adequate accepted standards of allergy practice while the child resides with the family. It is these children who had not responded to the treatments emanating from many schools of thought. They come from all parts of the country and compose the population of the Home.

DR. TUFT: The last paper on this afternoon's program will be presented by Dr. Peshkin.

### CLINICAL RESULTS OF THE REHABILITATION PROGRAM

DR. PESHKIN: We regard intractable asthma as severe, perennial, asthma requiring frequent hospitalization. It does not respond to the accepted standards of allergy practice in the child's own community. I wish to state as a result of the work of the Home a progressively increas-

ing number of physicians have discarded their antagonism, if not their nihilistic attitude to "parentectomy" for the humane and realistic approach to the treatment of intractable asthma. Most of the children who come to the Home are pale, undersized and have varying degrees of chest deformity. They are bewildered, overdependent, gripped with fear and emotionally immature.

The life situations, evaluation and management of asthma and other forms of allergy are not identical for children and adults. We are really dealing with different problems when handling asthma in children. We cannot call the child a small man or a small woman. The treatment of the child includes everything that childhood encompasses.

No mention has been made of the period of time treatment of the suspected intractable asthmatic child should be maintained. If no improvement is seen after one year, hospitalization should be considered. Moreover, if steroid agents must be used constantly to avoid troublesome asthma, then that child is intractably asthmatic. Of course, not all intractable asthmatic children can be controlled by steroids. Should steroids be used for long uninterrupted periods of time? The answer is obviously, "no," if complications or irreversible processes are to be avoided.

Although "parentectomy" deals essentially with control of emotional factors, I do not believe that asthma occurs initially without an immunological basis.

With asthma as the diagnosis, it is easy to understand (given certain conditions) how the role of psychogenic forces may retard or prevent recovery. Thus, psychogenic factors may be sufficiently disturbing to the child to cause him to hold on to asthma for his own special needs. Every child has his own motives for holding on to asthma. In most instances he is not consciously aware of the reasons. Psychotherapy may arouse feelings to the point of aggravating existing severe asthma.

The whole problem of the role of psychogenic disturbances in children, especially those with allergy commencing during infancy, is of more importance in these cases in which treatment is adequate but there is no response. Maternal rejection has been said to be at the root of the intractability of the illness. The concept of maternal rejection should be supplanted by that of parental engulfment ("The Cronus Complex"). This has been clearly described in a study of a patient whose childhood allergy extended into adult life. The psychogenic aspects of the disturbance were largely resolved through psychoanalysis. The interviews were recorded verbatim and were published without editing or dramatization with special reference to the mother-daughter relationship by our Chief Research Consultant, Dr. Harold A. Abramson. The data are presented in an interesting volume, "The Patient Speaks," Vantage Press, New York. As an allergist with some measure of psychological interest and orientation, I do not hesitate to recommend this book to all of you. When you finish reading it you cannot help but get a clearer picture of this phase of our work.

Some allergists have become oriented in psychiatry in order to become better equipped to treat the disturbed child with chronic asthma. In these children there is no more reason to exclude emotional factors than there is to exclude physical factors. We treat the total child.

I plan to discuss (1) the sex distribution, (2) the incidence of the age of onset of asthma, (3) the incidence of improvement of the children while at the Home and after their return to their own families, (4) the

minimum period of time necessary for residency at the Home for optimum benefit after return to their families.

*Sex Distribution.*—This series consists of 206 patients, 137 boys and sixty-nine girls. Thus, the ratio of boys to girls is 2:1. This ratio was first noted in 1926. From an administrative point of view, this ratio is important.

We were able to assemble two separate groups from this series, one group with and another group without pollen allergy. There were 103 children in group I (nonpollen sensitive) and a similar number in group II (pollen sensitive). In group I there were fifty-nine boys (57 per cent) and forty-four girls (43 per cent). This gives a ratio of boys to girls of 1.3:1. This ratio is of interest and should be remembered. In group II there were seventy-eight boys (76 per cent) and twenty-five girls (twenty-four per cent). Here the ratio of boys to girls is 3:1.

You may now appreciate the administrative problem with respect to the admission of boys who are pollen sensitive. What the striking difference in the ratios of boys to girls for the two groups mentioned means may be found in a statistical study of the asthmatic children who came to the Home during the last ten years from sections of the country other than the New York area. For the moment the figures suggest that when asthma in the children of group I is aggravated during the cold months the ratio of boys to girls tends to become equal. The figures for group II suggest that the occurrence of pollen allergy in boys poses a greater liability for intractable asthma than it does in girls.

*Onset of Asthma.*—The incidence of the age of onset of asthma in this report is based on 150 children who were available for follow-up study for twelve or more months after leaving the Home. (The ratio of boys to girls for groups I and II for the 150 children approximates the ratio for the larger series of 206 children).

To summarize the data, 150 intractable asthmatic children were sent from the New York area to the Home where they resided for periods ranging from twelve to thirty-six months. These children were returned to their families and were available for follow-up study for periods ranging from one to eight years.

The ratio of boys to girls was 2:1 for the entire series. However, the ratio of boys to girls for the nonpollen sensitive group was 1.3:1 and for the pollen sensitive group the ratio was 3:1. These figures suggest, as noted, that pollen allergy in boys poses a greater liability for intractable asthma than it does in girls.

The peak ages of onset of asthma occurred at two and three years. Seventy-four per cent of the children of both sexes had their asthma begin before the age of six years. However, the peak incidence for the boys was 19 per cent in the four and five year range, and for the girls 13 per cent, in the second and third year range.

In the nonpollen sensitive group the boys commence with a peak incidence of onset of asthma at four and five years of age which is one to two years sooner than girls.

In the pollen sensitive group the girls commence with a peak incidence of onset of asthma at two and three years of age which is one to two years sooner than the peak period for boys. These figures suggest that the girls develop pollen allergy sooner than the boys despite the ratio of boys to girls in the pollen sensitive group, which is 3:1.

The incidence of relief from asthma for boys and girls of the pollen and nonpollen sensitive groups does not tell us too much with respect to individual variations of symptoms because the incidences are averaged. However, when a single patient's progress is charted every six months a clearer understanding of the fluctuations is obtained.

Studies covering the period of time necessary for residence at the Home for the determination of the optimum benefit after the children are returned to their families show the following:

1. Seven and one-half per cent of the children whose residence at the Home was limited to twelve months failed to obtain relief from asthma (relief less than 50 per cent is termed a failure). All of these children were returned to their families and showed a subsequent average incidence of failures of 15 per cent.

2. One and one-half per cent of the group of children who remained in residence at the Home from eighteen to twenty-four months failed to obtain relief from asthma. All of these children were returned to their families and showed a subsequent average incidence of failures of 3.5 per cent.

3. There were no failures in the children maintained at the Home from thirty to thirty-six months. After all of the children were returned to their families the average incidence of failures rose to nine per cent.

These numbers indicate that "parentectomy" for twelves months for children with intractable asthma is inadequate for optimum rehabilitation after their return to their families; and that "parentectomy" for thirty to thirty-six months for the more troublesome cases does not appear warranted because of the relatively high incidence of failure after their return home. However, "parentectomy" from eighteen to twenty-four months appeared to be an optimum period of time for optimum rehabilitation after their return home, and so from an institutional point of view is regarded as the practical period for "parentectomy."

The average incidence of failures for the total series of 150 children was 1 per cent at Denver and 7 per cent, after return to their families.

You may wish to know some of our experiences on the influence of "parentectomy" on the other forms of allergy associated with intractable asthma.

Perennial allergic rhinitis tended to remain unchanged with too many patients despite rhinological consultation and treatment. Hyposensitization treatment with various inhalant extracts including pollen has not helped to clear or markedly alleviate the long standing and more persistent types of allergic rhinitis. Yet the asthma in these children is cleared or markedly relieved. Whether the psychogenic disturbance in persistent or intractable allergic or vasomotor rhinitis is more deeply rooted than it is for intractable asthma is a moot if not interesting question. We do know that "parentectomy" is not the treatment of choice for allergic rhinitis refractory to standard allergy practice. We do know that these patients are prone to develop nasal polyps. Moreover, these children, after return to their own homes, are more likely to have a recurrence of troublesome asthma than the children with very little or no disturbance with the nasal passages.

Children with chronic eczema of any origin do not do as well here as one might expect. As a matter of experience the rash in some of the patients has flared up one year after admission to the Home and long

after the asthma had cleared. The rash is usually dry, thickened, fissured and often lichenified, and usually found in the antecubital and popliteal fossae. Diet alone may at times control the exacerbations but fails to clear the rash. The rash may be resistant to any type of local remedy or may improve or clear spontaneously. The comment about psychogenic disturbance and perennial allergic rhinitis made above may also be applicable for chronic eczema here. This is another area where teamwork between the various scientific and clinical disciplines may well be integrated to determine why we have not been able to handle eczema better than we have so far.

Gastrointestinal allergy, urticaria and angioedema pose no problem since these conditions with respect to prophylaxis, or control, are known to the patient or are easily managed, and besides tend to clear spontaneously not long after the child has been admitted to the Home.

Hyposensitization therapy was found to be unnecessary for about one-half of the cases. For the other children, injections of pollen and mold extracts continue to be indicated as they were at their own home. The symptoms may be hay fever rather than asthma. However, at home the injections failed to give relief and often aggravated the asthma on a nonspecific basis. These children, after living in the Home a short time, accept injection therapy with benefit. Following return to their own homes, pollen therapy may be unnecessary for a number of cases since the symptoms of pollen allergy may not recur. When injections are given for hay fever with or without asthma a positive response is now obtained. When asthma persists especially in the nonpollen sensitive group intractability recurs in about two per cent of the cases. It is important to recall that all of these children prior to the admission to the Home had had adequate allergy management.

Food allergens more than other allergens play all kinds of tricks and some are bizarre, indeed. Some are so bizarre that psychogenic factors must be seriously entertained. Intolerance to one member of a biological food group tend to change to tolerance and often rather quickly. However, sensitivity to a biologic food group, such as the fish, cabbage or nut family, or extreme hypersensitivity to eggwhite, may persist long after the child leaves the Home in Denver.

Susceptibility to respiratory infections is important because so many of the children in this series were so afflicted before admission to the Home. Many were tagged with a diagnosis of "infectious asthma." When they come to the Home in Denver (although during the winter) the dramatic relief from asthma is indeed striking. Worthy of note is the frequent absence of asthma during an acute respiratory infection. Children do get "colds" while at the Home, but with much lower incidence than that experienced before admission. Most of the troublesome recurrences of asthma encountered in these children after return to their families have been induced by acute respiratory infections.

The incidence of status asthmaticus at the Home is strikingly low. In view of the high incidence prior to admission the sudden decrease is of great significance. In this connection it should be recalled that all the children on admission to the Home had chronic bronchitis, emphysema and chest deformity of varying degrees. Two or more years after they were relieved from asthma the picture may reverse itself to normal chest configuration.

A brief comment about steroids in children with intractable asthma.

From the standpoint of management the picture during the last four or five years has changed. It is not of import, if not amazing, that at the Home prior to the steroid era we had significantly fewer and less difficult problems to handle. Then, we had no deaths from asthma, an experience covering more than ten years. During the last three years with few exceptions the children who came to this Home had been on steroids for much too long a time. They were sent here because steroid therapy failed to check the asthma. During the last three years we have experienced three deaths due to the tissue changes induced by steroid use. These deaths and the post-mortem studies will be the subject of a special report.

Today the children at the Home are slowly weaned from steroids, but we stay alert to counteract threatening stressful conditions such as, physical trauma with great pain, surgery, infection and shock, with an increase of steroid dosage and the addition of antibiotic agents where indicated. It is believed that this regime gives the patient a more effective opportunity to overcome the stress situation and its implicit dangers.

Successful rehabilitation of the intractable asthmatic child is now an accomplished fact. We know how to rehabilitate this type of child, but many questions remain unanswered. There is hope that the proposed "Childrens' Asthma Research Institute and Hospital" will help solve some of these problems.

DR. TUFT: I introduce to you Dr. Bela Schick, our Chief Pediatric Consultant.

## SIGNIFICANCE OF ALLERGY IN CHILDHOOD

DR. BELA SCHICK: My remarks will deal with the significance of allergy in childhood. I begin with the statement that allergy is not a disease but a state of peculiar reactivity, a reactivity which is altered through previous contact with specific protein substances, other chemical substances, and finally contact with pathogenic bacteria and viruses. The reactivity is changed in relation of the time of appearance and of intensity. The increased sensitiveness in one of the characteristic symptoms of a pathologic allergic reaction.

In this broad definition of allergy a discussion of its frequency is useless and impractical because necessarily every individual is repeatedly under the influence of contact with such substances and becomes, therefore, allergic to them. We are all allergic in the broad sense of the word.

A practical evaluation of allergy is only feasible when we restrict our discussion to a certain group of what I call "syndromes of pathologic allergy," particularly to syndromes which you are so interested in as allergists; asthma, hay fever, eczema, etc., where the allergic reactions are annoying, undesirable, interfering with health and even endangering life.

The function of the allergist consists of finding the cause of the syndrome, so that the contact with the offending substance may be avoided. If the cause cannot be determined or the contact with the offending substance cannot be avoided, he must attempt to lower the intensity of the allergic reactions by medication or desensitization. We must realize that there is no real immunity as a result of this treatment. We do not achieve immunity. You become allergic and you are allergic all your life. We are fortunately able to desensitize many people suffering with hay fever or pollen asthma and some other allergens so successfully that they can live as normal individuals not allergic to pollen, etc. Desensitization is sometimes very difficult, and may finally become impossible; then we label such

a case as "intractable." Your Home demonstrates that even such cases can be successfully treated, improved, and brought back to health. They would have continued to suffer at their own homes because all methods of treatment, including change of environment and change of climate, had been ineffective.

You heard yesterday about the influence of the psychological and psychosomatic factors in the treatment of allergic conditions in the home environment. Dr. Peshkin introduced the term "parentectomy." I call it "familyectomy." The whole family has to be taken away, the whole environment must be changed. I was always impressed by the fact that when we in New York took a child with intractable asthma away from his home and put him in the hospital, the child was, within twenty-four or forty-eight hours, much improved. The only trouble was that when the child was sent home the attacks recurred. Dr. Peshkin conceived the idea. "Let's get the child away from the home for a longer period of time." The duration of separation is very important. Dr. Peshkin found that the only thing to do was to separate the child for several months; six months, twelve months, or even longer. The good results are not due to the change of climate, but to the separation from the parents and family.

We make theories to explain our observations. They may be wrong, but I am always in favor of creative thinking. A theory can, if not satisfactory, be abandoned or modified.

It might be something occurring in the cell itself, a change in metabolism, in its chemical make-up.

I was greatly impressed by the fact of the heart hormone discovered by Dr. Loewi, the Nobel Prize man, who found that if you stimulate the vagus nerve electrically, you produce at the end plate of the nerve a chemical substance which produces the vagus effect. This substance was later found to be acetylcholine (Dale). For a short time allergic symptoms have been explained as the effect of acetylcholine. But this theory had to be abandoned.

But there are other interesting observations. Another change of cell function is known. It is produced by treatment of mental disturbances. Sakel was the discoverer of the insulin treatment of schizophrenia. Sakel insists that his insulin treatment is different from treatment with electric shock. After getting a certain stage of insulin effect the mentally ill-patient (schizophrenic patient) acts normally. After the insulin effect recedes, the patient goes back to his original condition. The first effect of insulin treatment will be prolonged. In continuing the treatment finally the brain re-establishes its normal function. Apparently abnormal cell function becomes normal.

I am not able to give you a solution of the problems in allergy. The changes of reactivity must take place not in the serum but in the function of the cell itself. Our experimental studies must concentrate on the study of the cell. The Research Committee will have plenty to do in bringing progress in this respect.

Originally Pirquet and I expounded the theory that the allergic reaction is due to the antigen-antibody interference, or the interaction between the antigen and the antibody. This theory is still valid. The interaction produces a substance which is responsible for the symptoms. When the foreign substance, a protein, is first injected no antibody is present. This antibody has to be produced and brought into circulation. Now the interaction can take place. In case of repeated contacts the antigen finds

reacting antibodies present. When the antigen is again injected no time is necessary for forming an antibody. The antibody is present and therefore you can get reaction either immediately or at least after a short time. It is sometimes advantageous to prevent the antigen-antibody reaction.

These thoughts led to the use of ACTH and cortisone. But it may be a dangerous effect to interfere with antigen-antibody reaction. We prevent not only one antigen-antibody reaction, but we prevent all other antigen-antibody reactions.

In using steroids we interfere with the totality of antigen-antibody reaction, which can be harmful. The use of ACTH and cortisone must be carefully watched.

Now I can go to the facts of the influence of allergic reaction in childhood. For this purpose we have to consider the different age groups in which allergic reactions occur. In the first group is the infant, from birth to about fifteen months. Then we have the runabout child, between two and five years; the child of school age; and finally the child in adolescence and puberty. Asthma is really not so common in infancy. An infant rarely has asthmatic attacks on a non-allergic basis. Dr. Peshkin stated that an infant may have asthmatic symptoms on a nonallergic basis but due to enlarged tracheobronchial lymph nodes. This infant may become allergic later in life. The allergy could have been latent. Sometimes we hear wheezing or musical rales and this indicates the existence of asthma.

The symptoms of allergy in infancy are localized in two organ systems, the skin and the gastrointestinal tract. These two systems are the so-called shock organs. The skin may show urticaria or eczema. The gastrointestinal tract may produce vomiting, colic, diarrheoic stools. The substances irritating the skin include wool, silk, powder, soap, ointment, etc. Food is responsible for the gastrointestinal symptoms. Among food the chief offenders are milk, fish, wheat, egg and cod liver oil.

The situation of food allergy in infants is less complicated because the variety of food is restricted. As the variety of food is increased the difficulties of treatment increase. Other factors must be considered, for instance the presence of animals such as dogs and cats.

When the child grows older the allergic reaction of the gastrointestinal tract improves. This may be due to more effective function of the digestive secretion. The destruction of offending foreign proteins takes place more rapidly and the detoxifying function of the liver is more satisfactory.

After infancy the respiratory tract becomes the more frequent seat for allergic symptoms. Frequent attacks of respiratory infections may be present. There may be running nose, cough, bronchitic and bronchiolitic symptoms, pneumonia, and finally asthmatic attacks may occur. The child is less sheltered and more exposed to infections and inhalants. Irritating substances are entering the human organism by inhalation.

The above statement is also true for the adolescent child. One hears frequently that allergic symptoms and particularly asthma improve with the years and the child may outgrow the asthma. We may admit that in puberty the allergic symptoms sometimes improve possibly under the influence of hormones, but this is not always the case and it is better not to rely upon it. Therefore, the treatment of allergy, including asthma, should be carried out intensively in order to prevent the development of chronic forms of allergy, particularly of asthma. The chronicity of asthmatic symptoms may lead to organic changes in the mucous membranes and other parts of the respiratory tract. Such cases may be finally intractable.

Let us turn now to the incidence of allergy in the population. In the United States there are 50,000,000 children below the age of fifteen years. Twenty per cent or 10,000,000 of these children suffer allergic symptoms. Ten per cent or 5,000,000 of them need treatment; of these children, 2,500,000 are asthmatic. These numbers are large, showing how important the fight against asthma is. The physician must be forever on the alert in discovering and treating allergic and asthmatic symptoms. Home visits are of great importance, because through them a detailed history can be obtained. Also, the situation of the child in relation to its parents and other members of the household must be studied. Tension in the family is a factor that must be taken into account. Psychological influences may have an effect upon the child and these should be studied.

A question often asked is whether allergy is increasing. The answer is yes, but the increase may be due to the fact that our knowledge of allergy has improved. Thousands of new chemical substances are used in industry and in medicine. These new substances create new possibilities for allergic reactions. It is interesting to note that even the "miracle drugs" have unfortunate side effects producing new allergic reactions in the form of rashes, fever, and so forth.

It is not necessary to point out that asthmatic attacks in children may become alarming and need treatment and eventually hospitalization. Certain serious attacks which were intractable at home can be cleared up within twenty-four to forty-eight hours. However, it happens frequently that asthma attacks start again when the child returns to his environment. Dr. Peshkin realized that only a longer duration of treatment in a specially organized institution could bring about a lasting curative effect. The children suffering with chronic intractable asthma are really martyrs. They are not only bodily but mentally sick, sad and depressed by their apparently hopeless situation, losing entirely the joy of childhood. Every human being has only one childhood, which is short. Children in your institution found restitution to health, who would have gone to pieces staying in their own home.

Yesterday you saw these children blossoming again starting a new life. Not only the removal of unknown substances in the old environment, fresh air, and the best anti-allergic treatment are responsible for your success, but the psychological approach, love and cheerful surroundings, and a full understanding of the soul of the child are also an important decisive part of the curative effect of your marvelous institution.

Lucky are the children suffering with intractable chronic asthma who are admitted to your institution. Entering as unhappy, hopeless individuals broken in soul, they leave your Home rehabilitated and rejuvenated, looking forward to an enjoyable and useful life in society.

Dr. Peshkin, I cannot end my talk without congratulating you on what you have accomplished. You can well be proud of that which you have done. I have the history of Dr. Peshkin's accomplishments very clearly in my mind. I have worked with him from 1923 up to the present. That is quite a long time to know a person. Again, Dr. Peshkin, I congratulate you.

DR. TUFT: Thank you, Dr. Schick.

And now we would like to introduce the subject of the role of the regional consultants. As an example of what we encounter in the admission of children, I should like to read a letter which was sent to an in-

terested individual in New York. It was referred to us. "Dear Mr. Grady: Concerning telephone conversation as of this date, I am hoping you can help my son. He has had asthma ever since he was six months old. He is almost eleven years and in all his years he has had asthma sickness most of his eleven years. I have had doctor after doctor check him and examine him and no medicine they gave him has helped him for long. He has had oxygen, steroids, cortisone, et cetera, which helps him a little and then he gets the attack again. This winter his asthma seems to have gotten worse. As of this date it's nine weeks since he has been at school. He gets up in the morning and gets the asthma attack. The truant officer of his school recommended you. Can you help him? Please advise me."

When we get such a letter it is difficult to know, despite the parents' interpretation of the problem, just what the problem really is. Is it one of failure to respond to treatment or is it a question of not providing the correct treatment?

We have been, in general, dissatisfied with the admission of the children because we have been dissatisfied with their pre-admission evaluations. We, therefore, conceived the idea of utilizing your help, the help which you can give us as Regional Consultants, because of your background in the field of allergy, your training and your knowledge.

### ROLE OF REGIONAL CONSULTANTS IN THE ADMISSION OF CHILDREN

DR. PESHKIN: Dr. Tuft told you of our dissatisfaction with the intake admission procedure. You have in your kits a new history form. But before going on I wish to say that the Board of Trustees gave me the pleasant privilege of activating our Regional Consultant Plan. Participation in the evaluation of the new admission procedure is voluntary.

Rather than submit the children to the usual routine practiced by the social service agencies throughout the country, we allergists, by assuming the responsibility of processing the admission application, would serve the best interests of the patients. We have a job to do and that job is to get to know these patients and their families. With such a background of experience it becomes easy to launch an experiment. This is a pilot study and the Regional Consultants are part of this study. I have every reason to feel you men as allergists, are interested in the intractable asthmatic child. This child needs your sympathy and guidance as well as your continued attention.

In order to insure the success of this study, it occurred to me that we should get the physician, in this case the allergist, to process the applications. The responsibility really belonged there in the first place.

Your major interest is and shall always be the patients, the parents, and their feelings.

The number of admissions to the Home per year is about sixty?

DR. TUFT: Seventy-five.

DR. PESHKIN: And that includes admissions from all over the country. I think the number of applicants that come from the metropolitan area of New York is about twenty-five. We have about twenty-five Regional Consultants in the New York area so that one Regional Consultant may not be burdened with more than one case a year.

Here is what we intend to do. The patient makes the application directly to the Home in Denver. This is a special application form for the parents

only. Then the Home in Denver will send it to a Regional Consultant. He will be asked to fill out the special form for the Regional Consultants. There are spaces for a history and two physical examinations, which, if necessary, may be done on two different dates. After a few years, data collected in this way from the Regional Consultants, may evolve into a more efficient admission procedure.

The admission of these children depends on your evaluation and recommendation. After you have completed the history and examinations of the patient and forwarded the completed form to the Medical Director, I am sure that in almost all instances your recommendations will be approved.

Monthly you should receive a medical report. In order to participate fully in the program, it is advisable, if not necessary, to interview the parents from time to time. This is called "under-care supervision." This helps the parents to be relieved of concern, anxiety and tension about their child during his residence at the Home. To assist you in making the parent feel more secure, the Medical Director will send you, besides the medical report, such other information he deems would be helpful to you and the parents.

The kit also contains a second form covering the psychological aspects. I suggest your secretary or nurse make the necessary appointment with the parent and have her fill in the answers.

A special situation exists in the New York area. The Board of Trustees of the Home has given Dr. Abramson and me a grant for one year to set up a Parent Discussion Group. The purpose of this pilot study of group psychosomatic therapy is to provide a special kind of "under-care treatment." Formerly parents went to the social service agency. This type of treatment presented some difficulties. We hope to get a uniform overall view of parental problems and feelings through this discussion group. I suspect that papa is going to be resentful at the beginning. But later in the proposed fifteen sessions I think papa will slowly slip into the group activity and will want to know what it is all about.

The group discussions will be recorded verbatim and transcribed. Dr. Abramson will be the group leader. I will give the parents my analysis of the medical and psychological reports which I receive from the Home. This will be beneficial for the parents and it will be interesting to learn what they do with this material.

After the pilot study is completed we plan to assemble the material and write a brochure on psychosomatic therapy so that the Regional Consultants in other areas of the country may also conduct similar study groups. This brochure may also assist allergists to conduct group sessions for patients from their own practices.

Finally may I ask all of you please to help me to make this new project an outstanding success.

DR. TUFT: Dr. Peshkin covered the field carefully and thoroughly. However, The Psychological and Social Evaluation form needs some clarification. We require this information for many reasons, not the least of which is the management of these children. There are certain types of children who cannot relate very well in the Institution. Children with very low IQ's, for example, seem not to be able to manage themselves. We can handle them, but it is difficult. We have about 400 applications or inquiries per year. We can pick and choose the type of child who may respond best to therapy. Children who are actually psychotic, and we do

get that kind, would not do well in the Home. We are willing, as Dr. Young said yesterday, to carry on with those children who may have psychotic or near psychotic episodes after they get here. If we know of these conditions before admission to the Institution, we prefer not to accept the case.

For purposes of clarification of this particular part of the program, I would like to call upon our Supervisor of the Counselling Services, who is concerned with the evaluation of these applicants from the standpoint of counselling therapy. I present Mr. Lawrence C. Johnson.

### SOCIO-PSYCHOLOGICAL EVALUATION OF CHILDREN FOR ADMISSION

MR. JOHNSON: I want to begin by making a brief summary of why we feel the psychological form is necessary and valuable. We can understand the child better when we know as many details as possible about his life, his history, his family, and his ways of reacting. This will help us in understanding the emotional factors in the child's illness. It will help us to understand the child as he is when he comes to us, a product of his own unique history and background. It will help evaluate what the effects of treatment might be and how they might be received by the parents. For instance, you have heard how some of these children cease being asthmatic on reaching Denver or soon after, and begin acting out undesirable forms of behavior. Perhaps the parents cannot accept this. Perhaps they will need special help to understand the child who is beginning to act out his emotional problems. The psychological survey will also help us know how we can best prepare for receiving the child at the Home since we will know some of his adjustment problems. Very important is the fact that the process of getting together the information should help the child and parents prepare for separation. It should give them an understanding of the child's illness, and, what it will mean to the child in residence at JNHAC. The survey will also help you to determine and transmit to us the parents' and the child's real feelings about separation, the illness, and about coming to the Home. And last but not least this information will help us to formulate some hypotheses regarding emotional factors in asthma, hypotheses which we hope will be able to test out.

The questions in these long and seemingly cumbersome forms are divided up into sections. One section deals with the child's attitude toward his asthma, the family's attitude toward his asthma, and special situations noted to precipitate attacks. Another section deals with the emotional developmental history of the child; the family background; the current situation of the child; what goes on in the home, how the family is fixed financially, and how they get along as a group. And again, we are interested in the attitudes toward placement on the part of the parents and the child.

It has been pointed out repeatedly that separation is a two-way road. The child leaves the home and comes to JNHAC and the family in some instances feels it is deprived of this child. It does not quite grasp the real advantage to be gained. How do they feel about it? They should be helped.

The first section is devoted to the child's attitudes toward his asthma and the second section, the physical developmental history of the child. You have all had experience in getting this information together. This should not be too much of a problem.

For the section on emotional development, I think you may probably

have some trouble getting the information from the families. We would like to have as much of this information as possible because these answers are meaningful. We are particularly interested in the anxieties that the child displays, as Dr. Young mentioned yesterday. We find that these children have many anxieties. If we have advance knowledge of these anxieties we can then move more rapidly to help the child handle them.

Concerning the school situation, we want to know in as great detail as possible how the child gets along academically and socially; and we would like to have your estimate of the child's ability.

There are also questions about nail biting, finger sucking, and so on. Did the child have bad and disturbing dreams?

We want to know the living conditions, if the information is available, how the child feels about the economic condition of the family. We would like to know how the matter of channeling money has been handled by the parents and the child. We want to know if he is part of any organized group and how he gets along in it. I feel that in this particular section the parents' description of the child is one of the more important questions we would like to have answered.

Family background is mostly self-evident except for the relationship between the parents and their personalities, and that should be gone into. We ask how the physician feels this may have some bearing upon the child's present problems.

The term "familyectomy" has been used here. We found rather frequently that the presence of a grandparent or an uncle or an aunt within the family could be a rather disturbing factor, and we are quite interested to know whether there are other family members within the constellation, and if there are, what sort of role they appear to play, and how the child may be using grandma or grandpa as against mother and father.

We are particularly interested in finding what are the "real reasons" for wanting the child at JNHAC. We have long had the feeling that many youngsters are sent to the Home, or attempts are made to get youngsters into the Home, as a kind of placement for an annoying, disturbing, antagonistic, semi-delinquent child. We would like to know these things. It does not necessarily mean that the child will be refused admission to the Home, but these are the things of which we should be made aware before the child gets to us. It gives us an opportunity to know what to expect so that we can brief other people.

We would like to know what fantasies the child has about being sent away from home. The question was brought up yesterday, "How does the child feel about abandonment?" Some conversation indicated we infrequently sense that children feel they are being abandoned, but sometimes they do feel that way, based on perhaps some rather realistic notions that they are being sent away because they are naughty children, not because of their asthma; and this is the group we would like to learn more about.

We would also like to know, and I think this is quite important, what sort of responsibilities for the child's treatment, while the child is with us, the parents appear to be willing to accept. We would like to have your evaluation as to whether or not the parents' verbalizations of "responsibility" could be a product only of their present anxiety concerning the child and their wish to get him into the Home. It is necessary to know whether or not the parents appear to have some understanding of the

part they play in contributing to the child's asthmatic condition. And we want to know, "Do they seem ambivalent about placing the child?" I would suspect that every parent does, though you might make an assessment of the degree of ambivalence. And last, we want to know in your opinion whether they will be able to go through with placing the child in the Home for the necessary duration of the stay and whether or not they will be able to abide by the rules that the Home finds it necessary to set up concerning communication with the child, the things they can and can't do and write and say.

DR. LEON UNGER: It is a long questionnaire. I would estimate it would take three or four hours to fill it out and do a good job on it. It seems to me that a lot of these things could be answered by someone other than the physician. Could not the social worker fill out this form, or at least part of it? Why must the physician spend his time asking questions like that?

DR. TUFT: In direct answer to the question, if you could not do it at least your secretary or your nurse or someone who has a little time in your office could do it. We prefer not to have the social worker become involved, unless it is under your direction. Someone mentioned earlier that the form can be filled out by a medical social worker at the local hospital. This is perfectly all right; there is no question about that.

DR. SAMUEL J. TAUB: This is an excellent form and I think that we would learn a great deal from our own evaluation of the parents by paying some personal attention to getting the data, even if we do it in two ways. I would do it by having a preliminary secretarial interrogation followed by my going through areas of particular interest. I am not clear as to whether or not this is to be used in your admission evaluation or is it to be used in a larger sense in the total evaluation and treatment of the child? It does not really make a great deal of difference. I suppose it might be used in both ways, but it would seem to me that the psychologists, who are better qualified, perhaps, to get the kind of information that this requests, would probably be better equipped to do this after the child is admitted, and with much less time than it might take someone else. However, we as consultants could submit our considered opinions as to the admissibility of a child, weighing in even some of our parental evaluation, which would not be as complete as this form requests. This may be a fairly complicated kind of comment, I am really interested in knowing what the primary purpose is of this information. Is it for purposes of evaluating admissibility, or is it to be used for a total evaluation of the asthmatic child and its treatment?

DR. TUFT: There are some questions of admissibility in here, but very few. It is really to enable us to guide the therapy immediately upon admission. The medical form has a great deal of information, but simply saying that the chest is emphysematous and there is wheezing, with all the rest of the physical examination and all of the history, does not give us a picture of the child as we see him come into the Institution. It proceeds much better when every person who comes in contact with the child knows what to expect.

Dr. Peshkin indicated that houseparents in general are difficult to obtain. We try to obtain the type of personnel best suited for this position. The houseparents, for example, want to know what the situation

is. The child immediately moves into a living situation. They must know the situation. The administrator must know it. The Medical Department must know it. So, in general, this has more to do with the progress of the child immediately upon admission.

Let us say that our policy does not permit the parent to accompany the child, because when the parent does come on rare occasions, it's quite a problem.

QUESTION: You mentioned something about the parents abiding by the rules of the Home. Can you outline some of the rules to us in case we are asked about them?

MR. JOHNSON: I can send you a list. Most of our rules are related to visiting. The visits are usually limited to two or more depending on condition during the child's stay. The duration of the visit may be ten days, counting the day of arrival and day of departure. Medical permission must be obtained before making the visit. The child may not go away from the Home overnight. He may leave during any day with the family if his physical condition allows it, and stay out all day. This is difficult for some parents to accept. They want to see their children every two weeks or something like that, and across my desk almost every day come letters like this: "On February 21st John will have been with you six months. I understand I may visit him after he has been there six months. I'll be there February 21st." Now February 21 actually is a very bad time to come because we do not take the child out of school for the purpose of these visits. They can see the children only for short periods at that time. So then I must respond that the child cannot leave school and so on.

Regarding telephone calls, we attempt to limit them to one each month. We feel it is wiser for the child to place a collect call from JNHAC to his home instead of having the parents call him as it may be necessary to go searching for the child all over our seventeen and one-half acres.

Regarding packages, both administratively and psychologically we feel it is wisest for the child to have one package per month, no more. We also feel that packages should not contain food, nuts, chocolate, or as some parents have done in an attempt to evade the rules, extra money.

The parents have to realize that these limitations are best for the child and we are currently in the process of making a mimeographed form of what the rules are, which should come to you as Regional Consultants, so you can discuss with the parents the necessity and wisdom of abiding by the rules.

QUESTION: How much responsibility do the parents give you? Suppose a child had an attack of appendicitis; do you have to call the parents before you take action?

DR. TUFT: We have the full legal and moral responsibility for the treatment of the child while he is with us. However, as a matter of policy, whenever anything serious happens or anything happens that requires hospitalization away from our Institution, be it appendicitis or pneumonia, we call the parents directly at that time.

As a summary for this procedure, first the parents or referring physician sends the application or inquiry to us. We send the application form to the doctor or the parents for the parents to sign and return to us. When it is received we make the referral to the Regional Consultant. The Regional Consultant in turn accomplishes what is necessary and re-

turns the form to us. We take it to the Admissions Committee and get approval or disapproval. If approved, the child is admitted.

Frequently emergency admissions are requested. I suppose there are occasions when these may be considered. We can get approval immediately from our Admissions Committee by telephone should such a thing happen, but we feel that in general, particularly where hospital facilities are available in the home area, it is wiser to take these children to the hospital in the home area. These children may have suffered for five or six or eight years and it is difficult often, to determine whether another week or two will make that much difference. From the standpoint of the adjustment of the child to the Institution, it is preferable to take a little time and work with the child and the family so that they undersand what they are getting into. We have had occasions where the nature of the situation made it necessary for the child to be sent here quickly. Then we found that we had serious problems of adjustment. The child never really understands why he was sent here and the parents never really understand it. They look upon it as another hospitalization period rather than a whole new procedure of rehabilitation, which I think is important.

DR. HALPIN: How is transportation handled?

DR. TUFT: Transportation is handled by the parents paying for the original transportation. If the family is destitute, some way is found to bring the child here. The home community usually can get some sort of a sponsorship. Also, we require some plan for the return transportation be set up immediately upon our acceptance of the child. This has been done here in Denver for many years, and it is done for a purpose. We have had occasions when the family said, "Keep the child. All right, you're doing a good job. Keep him."

QUESTION: Suppose we feel a child should not be admitted, what should we do?

DR. TUFT: Almost without exception the opinion of the Regional Consultant will be honored. If you feel that the child should not be in the Institution because he does not fulfill our criteria for the admission of an intractable asthmatic child, then generally he will not be accepted. The refusal will come from us so that the responsibility for the refusal is ours.

As I told you, we have a physical therapist who comes to the Home and teaches breathing exercises. We have prevailed upon her to come down this morning and demonstrate some of these exercises for us. Mrs. Franz, do you want to come forward now?

### DEMONSTRATION OF BREATHING EXERCISES

MRS. BETTY K. FRANZ: We are going to demonstrate the breathing exercices that all of the children at the Home can do before the onset of an attack. If they can catch themselves fast enough and do the breathing exercises, in most cases they will prevent an attack. These exercises have been used on the Continent for some time. We have been using them at the Home for just the past year and a half. Up to now we have had good results with the children and the exercises. There are a lot of these exercises, so we have selected some to show you.

(At this point Mrs. Franz, with the aid of Michael, one of the boys from the Home, demonstrated various breathing exercises that are used at the Home.)

# TREATMENT OF GRASS POLLINOSIS WITH A SINGLE ANNUAL INJECTION OF EMULSIFIED EXTRACT. IV.

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THE SUBJECTS of this communication, the 383 patients treated for grass pollinosis with a single visit emlusion injection, were, in many respects an unusual group. Almost all were volunteers for repository injections in that each patient seen at my office over a period of one year was given a free choice. Patients taking treatment with extracts in saline could, if they liked, cease treatment on the day of interrogation, or could continue until the date set for the repository injection if they chose to change. Such injections were to be given between January 30 and June 10, 1958. New patients seen during the same time could take preseasonal treatment of the conventional type, change to injections taken perennially at intervals of four to six weeks after the season, or they could at any time between the dates given, come in for a repository injection.

The physicians of new patients referred were informed that conventional injection treatment could, as usual, be initiated and continued by them with annual re-evaluation studies by us, or else the repository injection could be given, preferably between the dates given. Incidentally, physician-acceptance of the single visit injection for themselves as new patients or for the members of their families was unanimous.

For new patients who first came to the office after April 15, the repository injection treatment was advocated because preseasonal treatment at so late a date could, in the light of experience, give them little immunity.

All patients were informed that there would be no charge for office visits between May 25 and August 1, should any symptoms of any type appear, irrespective as to whether they required oral or other medications. Those patients sensitive as well to ragweed pollen or to house dust or to both and scheduled for repository injections would in any case be able to give us progress reports, since the repository injections for the ragweed pollen would be administered from May 1 to August 15, 1958. During the interval represented by these dates, 722 patients (including thirty-six given a second ragweed pollen emulsion injection) were treated with such repository injections for ragweed pollinosis. Between the dates of October 8, 1957 and September 15, 1958, 594 patients were treated with house dust repository injections. Those of the latter two groups of patients not given grass repository injections but sensitive by skin test to grass pollen were therefore also seen during the grass pollen season. Notes were made of those who presented typical symptoms, so that the difference between the seasons of 1958 and those of 1959 following grass pollen repository injections to be given next spring could truly be evaluated.

TABLE I. AGES OF PATIENTS BY YEARS

| Age in Years | 1-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 |
|---|---|---|---|---|---|---|---|
| Number of Patients | 27 | 134 | 70 | 59 | 62 | 23 | 8 |

Seventeen of the 383 patients did not communicate with me during the season. They were not treated for ragweed or house dust sensitivities. As of the date of the tabulation of these results, they are on vacation or away from home. To keep the statistics uncluttered, they are for tabulation purposes, for the moment, classified as failures. In other words, the results of repository injections are put in the worst possible light.

For the same reason, any patient who has had any injection of grass pollen, although only one such injection, say the first of a series of routine injections during the previous twelve months, was classified as having had previous treatment. On this basis 310 patients are so classified. The remaining seventy-three had never taken injections of pollen extract of any type.

For the criteria of the syndrome of grass pollinosis, we set the limit at three years or more of undoubted symptoms occurring during the grass pollen season and corroborated by skin, conjunctival, or other tests. Many of the patients listed as having taken traditional treatment were seen as "new" patients during previous grass pollen seasons and the diagnosis was therefore not only made often by them, but also by the referring physician and by us. The usual pressures, especially of patients who wished repository injections for tree or ragweed pollinosis, made it necessary for us to accept for treatment ten patients with histories of symptoms for only two of the previous summers, and one affected only during the previous June and July. However, the symptoms were so typical, the tests so clear-cut and the number so small, that we feel that these inclusions cannot truly affect the measurement of results.

The sex distribution was unusual in that there were 227 male and only 156 female patients. Given a choice, male patients are more frequently impatient of the multi-visit type of treatment and, not wishing to leave their work for frequent visits to the physician's office, take more quickly to the repository type of injection.

The age distribution of these patients was also unusual. Tree and ragweed pollinosis occurring respectively at the end and at the beginning of the school year cause patients difficulty at times when medical attention is easily procurable. Grass pollinosis interferes with summer vacations and affects patients when they should be enjoying themselves, usually in areas where medical treatment is not given by the personal physician and when attendance at a physician's office for injections could interfere with vacation activities. The repository injection for grass pollinosis is therefore particularly popular with those who are likely to be away from home during the summer months. Table I, which lists the distribution of

TABLE II. MONTH OF CESSATION OF CONVENTIONAL INJECTION TREATMENT

| Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Patients | 113 | 63 | 42 | 29 | 17 | 9 | 13 | 11 | 5 | 3 | 5 |

the patients by age, strikingly illustrates this point, in that 263 of 383 patients were between the ages of ten and forty.

The distribution of patients previously treated is also not that usually encountered. Many continued their conventional treatment up to the date of the repository injection. Table II illustrates this fact, in that 218 of 383 were in the process of taking traditional treatment up to three months before the repository injection was given.

From these numbers are derived the figure of 310 patients who have taken previous injection treatment and seventy-three never before treated. The number of months since an injection had been taken (although in one patient only one) was chosen as eleven to make certain that the patients in the "previously treated" group included those who have suffered symptoms during the previous grass pollen season of 1957. In actuality (as with the patients treated with the emulsions for tree pollinosis), the number who were failures in treatment were approximately equal in both groups. There is no point, therefore, in giving traditional treatment until the date of the repository injection, in that such "transition" patients apparently do no better than those never before treated.

In all, fifty-one patients (whose difficulties will be discussed in detail elsewhere in this evaluation) described symptoms. Of these, thirteen had never been treated and thirty-seven had had some injections during the previous twelve months. In other words, thirteen of seventy-three (approximately 12 per cent) of the previous treated and thirty-seven of 310 (approximately 18 per cent) of those previously untreated suffered symptoms, a difference not significant in this frame of reference.

In the treated group, the magnitude of the dose of aqueous extract and the date of its injection bore no relationship to the onset of symptoms, either by the date of their appearance or the degree of their mildness or severity. Seven patients in this group ceased treatment with extracts prepared in saline one to four weeks before taking repository injections. Their respective top doses were 80 P.N.U. (in two patients), 250, 700, 1000, and 5000 P.N.U. (in two patients).

Twelve patients ceased treatment during the second month preceding the single visit injection. Their respective top doses were 20, 300, 700, 1000, 1300, 2600 (two patients), 3000, 3100, 3300, 4000 and 5500 P.N.U.

Eight subjects took no saline extract injection after the third month antecedent to the repository injection. Their respective top doses were 50, 80, 250, 800, 2600, 3500, 4000 and 4100 P.N.U.

The five patients who stopped taking traditional injections during the

TABLE III. NUMBER OF PROTEIN NITROGEN UNITS INJECTED

| Dose | 500 | 600 | 1000 | 2000 | 2500 | 3000 | 4000 | 5000 | 6000 | 7000 | 7500 | 8000 | 9000 | 10,000 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of Patients | 1 | 1 | 1 | 1 | 10 | 23 | 1 | 162 | 9 | 1 | 102 | 1 | 2 | 68 |

antecedent fourth month respectively reached top doses of 10, 100, 500, 800, and 3300 P.N.U. The doses of the fifth month patients were 50, 150, 500, 600, and 4300 P.N.U. The only other patient in this group stopped treatment at the 300 P.N.U. level eight months before his repository injection was administered. Obviously previous treatment, if so it can be termed, had no effect on the patient's future clinical course.

Nor in this group could the size of the repository injection nor the date of its administration be related to symptoms. One patient received 5000 P.N.U. on January 8, 1958. Of the twenty-eight who received their injections during February, the dose of one was 3000 P.N.U., of eight, 5000 P.N.U., of nine more 7000 P.N.U. and of ten, 10,000 P.N.U. Of eight patients given repository injections in March, one received 3000 P.N.U. and five, 5000 P.N.U., and two others 7500 P.N.U. The last patient in this group received 10,000 P.N.U. on April 1, 1958. There is then no obvious pattern from which any conclusions can be drawn.

In those never previously treated, there was again no relationship between the size of the dose and the date of administration, although the doses were generally smaller, due to greater clinical and laboratory sensitivity. Of seven treated during February, two received 2000 P.N.U., four, 5000 P.N.U., and one, 7500 P.N.U. Of four treated during March, two received 3000, one, 5000, and one, 7500 P.N.U. Only one patient in this group was treated in April, and with a dose of 5000 P.N.U. One last patient received only 1000 P.N.U. on May 8, 1958. By all criteria, these patients appear to be more sensitive and to have taken smaller doses, but the numbers and differences are not significant when viewed against the background of the group taken as a whole, among whom the doses were distributed as noted in Table III.

Nor was any relationship discovered between the duration of symptoms and a good clinical result. The group never previously treated had respectively suffered for two, four, five (two patients), eleven, twelve, fifteen (two patients), sixteen, seventeen, thirty, and thirty-one years. Of those previously treated, the duration was two years (two patients), three years (three patients), five years (three patients), six, eight (two patients), nine (two patients), ten, eleven, twelve, fourteen (two patients), fifteen (twelve patients, including all reporting "many years"), seventeen, twenty, twenty-five, thirty (three patients), forty-three and one for fifty years.

It made no difference in our results whether the patients suffered from allergic coryza or bronchial asthma or both. In those in whom we

achieved a perfect result, the diagnosis of the type of pollinosis is not important. In the previously untreated group, ten were typically hay fever patients, with one pollen asthma and another with both. In those previously treated and reporting symptoms, fourteen were diagnosed as allergic coryza, twelve as pollen asthma, and another twelve as both. Although an attempt might be made to extrapolate upwards the number of untreated patients in each category so that the numbers were comparable to those treated, the differences in the totals are so small as to be without significance.

As with treatment with extracts prepared in saline, it is impossible to predict who will do well. The results are not related to sex, age, type of pollinosis, duration of symptoms, sensitivity, previous treatment, size of repository dose, or date of its administration.

The repository injections were given to 164 tree-pollen-sensitive patients with no systemic reactions. But five systemic reactions occurred in the group of patients treated for grass pollinosis.

One patient, a man aged twenty-nine, and afflicted with tree, grass and ragweed pollinosis for seventeen years had never previously been treated. A tree pollen repository injection of 4000 P.N.U. was taken uneventfully on January 8, 1958. On February 5, 1958, the patient responded ophthalmically to 20 P.N.U./ml of grass pollen extract. He was given a grass pollen repository injection of 5000 P.N.U. He later reported that on his way home, he broke out in a mildly pruritic general rash which lasted in all three hours, requiring no medical treatment. He suffered from sneezing attacks daily for several days at the end of May and the first days of June during the overlapping of the two pollen seasons. He is classified as a failure in treatment, although no symptoms occurred before or afterwards (as of August 11).

The second systemic reaction affected a fifteen-year-old boy who had suffered from allergic coryza and bronchial asthma "since infancy." A repository injection of 3300 P.N.U. for tree sensitivity had been administered on December 18, 1957 with no symptoms then or during the tree pollen season. The grass pollen skin test was positive by pressure puncture and ophthalmically at the 40 P.N.U./ml level. On February 21, 1958, a 1000 P.N.U. dose of grass pollen extract was prepared for injection. After the second half, that is, 500 units, was injected, the patient broke out in generalized urticaria limited chiefly to the trunk and above the waist. Because of the history of bronchial asthma, nebulization with epinephrine 1:100 was initiated, although there were no pulmonary symptoms. The hives disappeared within ten to twenty minutes. The patient had no recurrence and no symptoms whatsoever during the grass pollen season.

The third systemic reaction occurred in a young man, aged seventeen, with a history of allergic coryza, present since infancy. Wheezing occasionally occurred non-seasonally. He had never previously taken treatment.

The pressure puncture test was positive, as was the ophthalmic test at the 20 P.N.U./ml level. A grass repository injection of 5000 P.N.U. was decided upon. During the injection, given on February 21, 1958, some small scattered hives appeared. The patient took Benadryl (diphenhydramine, 50 mg Parke, Davis & Co.). The urticaria disappeared in approximately ten minutes. The repository was continued, the patient taking the full dose with no further immediate symptoms and none during the pollen season.

The fourth systemic reaction occurred during the treatment of a woman patient aged twenty-eight who had suffered from tree, grass and ragweed pollinosis for "many years." A repository injection of 3300 P.N.U. for the tree pollens was given uneventfully on December 17, 1957 with a perfect result. On February 4, 1958, the patient presented a pressure puncture positive test to grass pollen and an ophthalmic test at the 80 P.N.U./ml level. A dose of 2000 P.N.U. was decided upon to be given in divided parts of 500 P.N.U. at twenty-minute intervals. Ten minutes after the last part had been injected, general urticaria appeared. The patient was given epinephrine 1:1000, 0.15 ml and a tablet of Diafen (diphenylpyraline hydrochloride, 2 mg Schenlabs). The hives gradually subsided and were completely gone in an hour. There was no recurrence and there were no symptoms during the grass pollen season.

The fifth reaction occurred during the treatment of a female patient aged thirty-four who had suffered from a grass and ragweed pollen and house dust sensitivity since early infancy. She had taken no previous treatment. The pressure puncture test was positive, as was the ophthalmic test at the 320 P.N.U./ml level. On March 25, 1958, a repository injection of 3000 P.N.U. was taken in six divided doses, following which the patient broke out into angio-edema. This was treated with epinephrine 1:1000, 0.15 ml and repeated in thirty minutes. The lesions then began to fade. Chlor-Trimeton Repetabs (chlorprophenpyridamine maleate, 8 mg Schering) tablets were prescribed to be taken at eight-hour intervals. The last signs, as palpebral urticaria, were gone in sixteen hours with no recurrence and no symptoms at all (as of July 16) during the grass pollen season.

Four of the five systemic reactions occurred in patients positive to pressure puncture tests. The ophthalmic tests were positive at the 20 P.N.U./ml level in two, at 40 in one, at 80 in another, and at 320 in the fifth. According to our modification of Loveless' categories, the first, third and fifth patients should have respectively received 2500 P.N.U. each.

A sixth patient, never previously treated and positive at the 20 P.N.U./ml level ophthalmically, took a 5000 P.N.U. grass repository injection on February 4, 1958. He awoke at 2 a.m. of February 5, 1958 with nasal congestion which recurred at 2 a.m. on February 6, 1958. There was no recurrence. He reported a perfect season.

TABLE IV. TABULATION OF PATIENTS PRESENTING SYMPTOMS

| No. | Patient | Sex | Age | Diagnosis | Years | Aqueous Injection P.N.U. | Tests—P.N.U./ml | | | Emulsion | Date | Patient Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | IC | P.P. | Ophth. | Total P.N.U. | Given | |
| 1 | LA | F | 11 | AC | 11 | 0 | + 100 | | 640 | 7,500 | 2-13-58 | Red eyes, runny nose, sneezing on 6-6-58. Relieved by Diafen. No symptoms since. |
| 2 | RA | M | 33 | AC&BA | "many" | 800 | +2000 | | 1,280 | 7,500 | 2-10-58 | Hay fever on 7-12-, 7-18-58. No symptoms since. |
| 3 | BB | F | 6 | BA | 2 | 80 | + 100 | | 20 | 3,000 | 2-25-58 | Eyes itchy, occ. redness, sneezing present for 21 days ending 7-18-58. |
| 4 | AB | F | 30 | AC | 4 | 0 | + 100 | | 20 | 3,000 | 2-25-58 | Nasal stenosis, itching. Relieved by Perazil and Diafen. |
| 5 | RB | M | 16 | AC | 5 | 2600 | + 100 | | 80 | 5,000 | 2-26-58 | Stuffy nose, sneezing 6-4 to 6-18-58. |
| 6 | RB | M | 15 | AC&BA | "many" | 700 | +2000 | | 10,240- | 7,500 | 2-24-58 | 7-10-58: Working on farm, had slight morning sniffles lasting up to one hour. No medication needed. |
| 7 | CC | M | 25 | BA | 15 | 80 | +1000 | | 80 | 5,000 | 1- 9-58 | AC began 6-5-58. BA on 6-20-58. Relieved by methyl prednisone. |
| 8 | DC | M | 11 | AC | 5 | 0 | | + | 20 | 1,000 | 5- 8-58 | Took Perazil t.i.d. from 6-2 to 7-6-58. Is improved over '57. |
| 9 | FC | F | 15 | AC&BA | "many" | 5000 | +2000 | | 10,240- | 10,000 | 2-25-58 | Occ. sneezing, no medication needed. Better than last year. |
| 10 | TC | M | 56 | AC&BA | 43 | 5500 | +2000 | | 5,120 | 10,000 | 2- 6-58 | Hay fever for 5 days ending 6-30-58. Morning and evening wheezing on 7-9-58. No further symptoms. |
| 11 | SC | F | 11 | AC | 5 | 50 | +2000 | | 5,120 | 10,000 | 2-17-58 | 7-1-58: Some sneezing each day for six weeks. |
| 12 | ED | F | 27 | AC | 9 | 3500 | +2000 | | 40 | 5,000 | 2-17-58 | 7-8-58: "Have had attacks during past week. Nose is runny, eyes itchy. I sneeze a lot." |
| 13 | CD | M | 36 | BA | 30 | 5000 | +2000 | | 10,240- | 10,000 | 2-10-58 | 7-21-58: Took trip West; one hour of symptoms late June in Reno. One hour mild symptoms in Montana. No symptoms since. |
| 14 | JD | M | 52 | AC&BA | "infancy" | 1300 | +2000 | | 10,240- | 7,500 | 2-19-58 | 7-7-58: Has "had it tough" 3-4 days despite rainy weather. No further symptoms. |
| 15 | AD | F | 49 | AC&BA | 35, 13 | 0 | | + | 80 | 5,000 | 2- 8-58 | AC & BA present all through June. Required no medication. |
| 16 | FD | M | 49 | AC | 31 | 0 | +1000 | | 10,240- | 5,000 | 2-18-58 | 7-8-58: Occ. "drippy" nose at night. "Definitely better than last year." |
| 17 | MD | F | 51 | AC&BA | 20 | 1000 | +2000 | | 10,240- | 10,000 | 2-13-58 | Severe itching of eyes first 2 weeks in July. No other symptoms. |
| 18 | JE | M | 15 | BA | 12 | 250 | | + | 80 | 3,000 | 3-11-58 | Symptoms began in early June. (Pt. plays up to 27 holes of golf regularly). |

TABLE IV. TABULATION OF PATIENTS PRESENTING SYMPTOMS—CONTINUED

| No. | Patient | Sex | Age | Diagnosis | Years | Aqueous Injection P.N.U. | Tests—P.N.U./ml | | | Emulsion | Date | Patient Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | IC | P.P. | Ophth. | Total P.N.U. | Given | |
| 19 | RG | F | 17 | BA | "childhood" | 4000 | +2000 | | 10,240- | 7,500 | 2-20-58 | Symptoms on 7-1, 7-4, and 7-21-58. Drove to Martha's Vineyard, stayed 1 week. Drove back 7-5-58. |
| 20 | WG | M | 15 | BA | 14 | 4100 | | + | 1,260 | 10,000 | 2-17-58 | 7-9-58: Occ. wheezing up to 5 times daily, relieved by nebulizer. Worst day 7-4-58. |
| 21 | DG | M | 7 | AC | "several" | 0 | +2000 | | 10,240- | 5,000 | 4- 3-58 | Sneezing began 6-12-58. Better than 1957. |
| 22 | LG | F | 16 | AC | 3 | 150 | +2000 | | 5,120 | 7,500 | 2-19-58 | 7-7-58: "Some" symptoms. |
| 23 | RG | M | 18 | AC | "many" | 2600 | | + | 160 | 5,000 | 3- 4-58 | 6-16-58: Sneezing for 1 week during overlapping of tree and grass pollen seasons. |
| 24 | PH | M | 8 | BA | 6 | 300 | +2000 | | 10,240- | 5,000 | 3- 5-58 | No symptoms except for wheezing only on 7-1-58. |
| 25 | AH | F | 53 | BA | 3 | 4300 | +2000 | | 10,240- | 10,000 | 4- 1-58 | 7-10-58: Sl. wheezing in evenings requiring anti-spasmodic medication. |
| 26 | MJ | F | 26 | AC | "many" | 250 | +2000 | | 10,240- | 10,000 | 2- 6-58 | 7-14-58: Sneezing for a few days. No further symptoms. |
| 27 | SK | M | 10 | AC | 3 | 10 | +2000 | | 10,240- | 5,000 | 2-27-58 | 7-22-58: Symptoms began 2 weeks ago. "Medication on hand helped immediately." |
| 28 | RK | M | 10 | BA | 10 | 20 | | + | 320 | 5,000 | 2-18-58 | Cough and wheeze on 6-25, 7-3, 7-17, and 7-25-58. Home during first three dates. Drove home from Cape Cod preceding 4th. Oral med. used first 3 times, Aminophylline suppository used 4th time. |
| 29 | EL | M | 20 | AC&BA | 17 | 3300 | +2000 | | 1,280 | 7,500 | 2-17-58 | 7-7-58: Morning sneezing and coryza lasting to 2 hours began 1 week ago. "Estimate 75% improvement." |
| 30 | SL | M | 38 | AC | 15 | 80 | +1000 | | 1,280 | 7,500 | 3-13-58 | 7-22-58: Mild symptoms began 2 weeks ago, sneezing every day. Symptoms while driving to Maine. |
| 31 | WM | M | 11 | AC | 8 | 3500 | +2000 | | 10,240- | 7,500 | 2-17-58 | 7-7-58: Had sniffles of approx. 1 week's duration while at summer place. |
| 32 | RN | M | 6 | AC&BA | 2 | 0 | | + | 80 | 3,000 | 3- 6-58 | 6-9-58: Brief mild asthma during last week in May. ?Overlapping tree and grass pollen seasons. |
| 33 | LN | F | 13 | BA | 5 | 500 | + 100 | | 10,240- | 5,000 | 3-18-58 | 6-24-58: One week of symptoms. |
| 34 | AP | M | 46 | AC&BA | 30 | 4000 | +2000 | | 10,240- | 10,000 | 2-10-58 | 6-25-58: Symptoms while haying. Wheezing one night, relieved by oral medication. |

TABLE IV. TABULATION OF PATIENTS PRESENTING SYMPTOMS—CONTINUED

| No. | Patient | Sex | Age | Diagnosis | Years | Aqueous Injection P.N.U. | Tests—P.N.U./ml | | | Emulsion | Date | Patient Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | IC | P.P. | Ophth. | Total P.N.U. | Given | |
| 35 | WP | M | 10 | AC&BA | 9 | 700 | | + | 320 | 5,000 | 3-13-58 | 7-22-58: Wheeze, sneeze and cough for two weeks. |
| 36 | AP | M | 15 | AC | "many" | 100 | + 100 | | 2,560 | 5,000 | 3-18-58 | Sneezing, postnasal drip until school closed 6-18-58. No symptoms since. |
| 37 | RR | M | 33 | AC&BA | "infancy" | 800 | + 100 | | 20 | 5,000 | 2-26-58 | 7-22-58: Mod. hay fever began on 7-4 while camping. Worse when on water 5 mi. from land, NW wind. Reoccurrence last few days. |
| 38 | JS | F | 15 | AC | 12 | 0 | + 100 | | 160 | 5,000 | 2-18-58 | "Running nose" on 7-9-58. Was "better than last year." |
| 39 | FS | M | 17 | BA | 15 | 1000 | +2000 | | 2,560 | 10,000 | 2-17-58 | Sl. attack during 1st week in June. Taking no medication. ?Overlapping tree and grass pollen season. |
| 40 | SMG | F | 38 | AC | 14 | 600 | + 100 | | 80 | 5,000 | 2-20-58 | 7-16-58: Nostrils blocked 10 nights. Exposed to shedding feather pillows. Takes Phenergan. No subsequent symptoms. |
| 41 | DS | M | 18 | AC | 11 | 300 | + 100 | | 1,280 | 7,500 | 2-26-58 | 7-8-58: Intermittent symptoms since early June. |
| 42 | PS | F | 33 | AC&BA | "childhood" | 0 | +2000 | | 10,240- | 7,500 | 3- 4-58 | 7-22-58: Eyes itchy for 1 week beginning one week ago. |
| 43 | JS | M | 11 | AC | "many" | 2600 | +2000 | | 2,560 | 7,500 | 2-21-58 | 7-8-58: 3 days of symptoms; has required medication last 3 weeks. |
| 44 | WT | M | 19 | AC | 5 | 0 | +1000 | | 1,280 | 5,000 | 3-12-58 | 6-26-58: Hay fever began 6-12, complete relief with Perazil. |
| 45 | RW | F | 51 | BA | 25 | 3000 | +2000 | | 5,120 | 10,000 | 2-10-58 | 6-24-58: No symptoms except occ. nasal stenosis on arising. |
| 46 | JW | M | 29 | AC | 17 | 0 | +1000 | | 20 | 5,000 | 2- 5-58 | Sl. sneezing end of May, 1st of June. Has sensitivity to tree pollen. |
| 47 | CW | M | 28 | AC | "many" | 15 | + 100 | | 80 | 5,000 | 2-24-58 | 7-22-58: Symptoms began 2 weeks ago while driving. Eyes itchy for 4 hours only. |
| 48 | MW | F | 42 | AC | 16 | 0 | | + | 80 | 3,000 | 3- 5-58 | 7-8-58: Symptoms began 1 week ago, affecting eyes and nose. Slight wheeze. Well indoors. |
| 49 | HW | M | 17 | AC | "infancy" | 0 | | + | 10 | 3,000 | 2-27-58 | Symptoms from 5-17 to 7-15, affecting nose only. |
| 50 | JY | M | 12 | AC&BA | 9, 2 | 3300 | +1000 | | 620 | 7,500 | 3- 5-58 | 7-22-58: Asthma up to 1½ hrs. since 6-1, with occ. free days and mornings. Relieved by Amodrine, ½ tablet. |
| 51 | RZ | M | 8 | AC&BA | 8 | 500 | +1000 | | 80 | 5,000 | 2-19-58 | 7-2-58: Wheeze this morning. Nasal symptoms for 2 weeks. |

A seventh patient, a man aged forty, never previously treated for grass and ragweed pollen sensitivity of eight years duration, responded positively to the pressure puncture test and ophthalmically at the 160 P.N.U./ml level. On May 2, 1958, he received a grass pollen repository injection of 5000 P.N.U. He stated on July 7, 1958, that although he had gone through the grass pollen season with no symptoms, his nose had been "blocked up" for ten days following the injection. This had, however, occurred on previous occasions not following an injection. The sixth and seventh patients do not in my opinion represent systemic reactions, but for tabulating purposes are included.

We subsequently gave 1374 patients one to two repository injections with only three additional systemic reactions, making the total so far for 1929 patients who have taken one to six repository injections eleven systemic reactions. This number includes two unprotected patients who have been described before and separately. It can be seen that almost all eight patients can generally be placed in the same category in sensitivity.

It is my belief that these same patients could probably never have taken aqueous injection treatment at the same dose level without reaction.

Our system for recording failures in treatment requires some explanation. Facts can be derived from figures, but only with difficulty from states which can only rarely be changed into percentages. Table IV lists a percentile result only when it came as an unsolicited statement made directly by the patient. The table, as did others in the series, lists each patient by number and first and last initial, and by sex (M or F). The age is then given in years and the diagnosis as AC (allergic coryza) and BA (bronchial asthma) or both. Then follow the years of duration of symptoms. The word "many" usually signifies more than ten but less than twenty. The majority lie between ten and fifteen years. The word "infancy" usually means under the age of six, and the word "childhood," the years from six to fourteen. Some patients cannot remember when the first symptoms were noticed. When certainly less than five years, the word "several" has been used. Then follows the top dose of extract in P.N.U. if previous treatment has been taken, or a "0" if the patient has never previously been treated by injections. The next three columns list the results of tests, intracutaneous, pressure puncture or ophthalmic. The latter, if preceded by a minus sign, signifies a negative test, a routine result in patients free of conjunctival symptoms. Then follows the dose of the emulsion in protein nitrogen units, the date when it was administered, and lastly, the patient's own comment. When the patient comment is preceded by a date, it is the date on which the patient reported. The remaining patients are not tabulated because in them there were no symptoms whatsoever.

A previous paper in this series has in detail described our method of "protecting" patients afflicted with pollen sensitivity and given in single visit but divided doses relatively large amounts of emulsified ragweed

pollen extract.[1] A second communication[2] tabulated the clinical results achieved in thirty-eight patients treated for ragweed pollinosis with material supplied by Loveless. In the third paper[3] were described the results of the treatment of 164 patients sensitive to tree pollens and treated with single injections of emulsified extract prepared in our laboratories and injected in accordance with several modifications of Loveless' technique.[4] A history of the treatment of pollinosis (1898-1958) in press[5] discusses the subject of treatment with extracts prepared in saline from the point of view of skin tests, dosage schedules, reaction rates, and "percentile" results and in detail the technique at present used for treatment with emulsion injections.

We are here concerned with an additional 383 patients sensitive to the grass pollen treated by single visit but divided doses of grass pollen extract emulsified in mineral oil according to Loveless' technique.[6] Of these patients we have no reports as yet on seventeen. If, again, as in previous papers, for statistical purposes we set as our standard of failure every symptom of any type whatsoever and however mild, then with these seventeen also included, the remaining 315 other patients presented no symptoms at all between May 26, and August 7, 1958, the extreme limits of our grass pollen season.

Of the 383 patients, 310 had taken some extract in saline injections during the preceding year. Seventy-three had never previously had injection therapy. Thirty-eight of the patients who had taken previous injection treatment and thirteen who had never been treated previously presented some symptoms. On this basis, if we wish to use percentages, we can say that 315 of 383 (82 per cent) of the patients enjoyed a symptom-free grass pollen season. Five patients suffered systemic reactions, none severe. All plan to continue with repository injection treatment.

The studies of Loveless, who pioneered in the field of using pollen extract emulsified in mineral oil, are amply confirmed in that the results were equal, if not superior, to those achieved by conventional treatment with extracts prepared in saline.

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# MANAGEMENT OF COMPLICATIONS OF ALLERGIC RHINITIS

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THIS presentation is predicated on the assumption that the reader thoroughly understands allergic rhinitis. It will be confined to a discussion of cases in which the diagnosis of allergic rhinitis has been made, the etiological antigens have been identified, indicated avoidance and sensitization therapy has been instituted, and the allergic factors may be considered under control, without the patient's obtaining relief. Nonetheless, it is elementary that the allergic factors must be controlled before all complications can be properly treated although this may seem a trite observation.

The most common complication is nasal obstruction which may be due to mucosal changes or bony obstructions, or both. In the majority of these cases relief may be obtained by proper allergic therapy. With the sole exception of removal of large polypi, no surgery should be considered until the antiallergic treatment has had its full effects.

Simple hypertrophy of the turbinate mucosa usually subsides when the allergic factors are controlled. Failure to obtain such results is indication for additional studies by the allergist, closer adherence to the prescribed regime by the patient, or both.

Bony hyperplasia of the inferior turbinates is not an unusual condition and may require surgical correction. Under local anesthesia an incision is made, starting on the lateral wall just above the turbinate attachment, down along the anterior tip, through the mucosa and periosteum to the bone; using septal elevators, the mucosa is dissected free medially and laterally, and freed from the inferior border; the hyperplastic bone can then be removed with bone scissors and biting forceps; the incision is closed with silk sutures and the nares lightly packed with three strips of dental baseplate wax. Removal of inferior turbinate mucosa is contraindicated.

Bony cysts of the middle turbinate also require surgery. When located in the tip I prefer to remove the entire tip with snare and biting forceps; but if one prefers to leave the tip, or if the cyst is in the medial portion of the turbinate, the turbinate should be infracted and the lateral wall of the cyst can be removed with biting forceps. In such cases the

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cyst margins should be cauterized with the electric cautery. Simply crushing the cyst with biting forceps is not adequate.

Septal deviations are easily corrected by submucous resection and I prefer the Galloway technique. Usually, such large spurs are present that it is impossible to separate the mucosa from the spur without tearing it. There is no danger of perforation if the mucosa is torn only on one side, but recovery is hastened by closing the tear; this can be accomplished fairly easily with a Stevens needle holder, a small full-curved Lane cleft palate needle and 0000 black silk. I make a small incision through one side, posteriorly, and inferiorly, with an angled knife, to provide drainage and prevent hematoma formation. I prefer three strips of dental baseplate wax in each naris instead of packing or leaving the nares unpacked.

Polypi are rarely present without an accompanying sinusitis, which is the second most common complication of allergic rhinitis. Indeed, it is often the severe symptoms of sinus infection that cause the patient to seek relief; and such relief must be given promptly. The history, examination, laboratory and x-ray studies should reveal that the patient has an allergic rhinitis with super-imposed acute infection. With adequate therapy the acute phase can usually be controlled promptly. When possible—and it is usually possible—this should be done without employing antihistaminic agents; they interfere with diagnostic studies. The patient should then be thoroughly studied and indicated therapy begun.

When a patient is first seen with a large polyp blocking the naris, Kuhn[1] has recommended injecting cortisone into the polyp. In my limited experience this causes some regression in approximately 50 per cent of cases; since there is no contraindication to the procedure, I employ it.

In the earlier stages, and less severe cases, adequate treatment will eliminate the infection, and proper regime will control the allergic factors, but the polypi will persist and will require surgical removal. In only one case have I seen a pedunculated polyp regress entirely. In these early cases the polypi are usually located in the middle meatus, originating around the infundibulum. They are easily removed by snare and biting forceps, but the bases should be routinely cauterized with the electric cautery. Polypi have a tendency to recur, and usually do recur when the factors causing the allergy are not controlled, or if the patient later discontinues the treatment. Adequate cauterization of the mucosa where the polypi originated causes scar tissue formation and prevents recurrence at that particular site.

The more advanced and chronic cases of sinus infection, with or without polypi, will not entirely clear up under any medical therapy. Patients usually come in seeking relief during an acute exacerbation and intensive therapy is often required to control the acute phase. Hormone therapy is of value in addition to the usual antibiotic therapy, chemotherapy, or both. I prefer prednisolone orally and good results are usually obtained

with 4 x 5 mg daily. Hormone therapy should be used very briefly in young patients but can be used more freely in older patients. Incidentally, hormone therapy has the advantage of interfering very little with skin tests, as compared to antihistaminic agents.

These advanced cases will require surgery; the more advanced the case, the more radical the surgery. They should be studied carefully and adequately. X-ray studies should always be made; additional information can be gained by injecting radio-opaque liquid into the antra and repeating the x-rays. Similar studies can be made of the sphenoid sinuses, using the Proetz displacement procedure.

In the less involved of the advanced cases, a naso-antral window is adequate; with drainage and ventilation, and continuation of the allergic regime, the antral mucosa returns to normal. More involved cases will also require anterior ethmoidectomy, particularly when polypoid mucosa prevents adequate drainage from the frontal sinus. Still more advanced cases will require radical antrum surgery, ethmo-sphenoidectomy and even radical frontal sinus surgery. It may be again emphasized that surgery should never be considered until the patient has had the full benefit of medical therapy for allergies. It must be also recognized that cases not relieved by such therapy will require surgery for relief, and should be given the benefit of surgery.

Perhaps this is the place to condemn the removal of tonsils and adenoids to relieve symptoms of allergic disorders. Many children require adeno-tonsillectomy, but all allergies should be entirely controlled before surgery is considered.

Lymphoid tissue is likely to recur in patients with allergies, particularly those who do not follow the prescribed regimen. Ordinarily, this is of little importance; lymphoid tissue, particularly in the nasopharynx, has a tendency to regress as the patient grows older. However, when there is sufficient hypertrophy to block the eustachian canals with resulting impairment of hearing, or lateral bands persist with symptoms following exposure to colds, surgery or radium therapy becomes necessary. If there is a large mass of adenoids, surgery is preferred. When there are only small nodules in Rosenmuller's fossae, I prefer radium treatment with the Crowe applicator; two to four applications of 36,000 mg/sec. in each nasopharynx at two-week intervals is adequate. Some patients with lateral bands can be adequately treated by application of 25 per cent silver nitrate solution; other patients will require surgical removal of the bands.

This introduces a discussion of serous otitis, which may be difficult to relieve. Any casual survey of the literature will reveal that we know far too little about this important clinical entity. My studies show that edema due to allergy blocking the ventilation of the eustachian canals, is the etiological factor in at least 20 per cent of my patients who fail to respond to treatment. The serous fluid must be aspirated at frequent intervals, at least once weekly. Presently my technique is to do a double

paracentesis with a 19 gauge spinal needle on a tuberculin syringe in the anterior-inferior and posterior-inferior quadrants, withdrawing fluid with each paracentesis. The patient remains in the chair for ten to fifteen minutes; then suction is applied with a McLaurin or Ferguson No. 0 suction tip. The double puncture permits better drainage; when suction is used, air is drawn through the other opening, avoiding vacuum pressure. If the fluid is not withdrawn during the serous stage, it may become thick and viscid, with greater impairment of hearing, requiring large tympanotomy and suction. If not recognized, these cases may develop adhesions of the tympanic membrane to the promontory, and permanent impairment of hearing. Cytological examination of the clear, serous fluid is valueless; but when the fluid is turbid, cytological examination should always be made. Eosinophilia indicates allergy. Serous otitis in a case of allergic rhinitis usually indicates the allergy is not under control; adequate drainage should be provided until the patient's condition is under control.

There are occasional cases of recurrent laryngitis associated with allergic rhinitis. These cases are easily explained while the patient is suffering with allergic rhinitis, but their recurrence after the causes of the allergy are controlled requires further consideration. Studies of these cases reveal they are often due to bad vocal habits or to accompanying bronchial involvement. The bad vocal habits are not always corrected easily—such patients do not change habits readily. The bronchial involvement may be even more serious.

Asthmatic bronchitis and bronchial asthma should not be considered as complications of allergic rhinitis but as concomitant manifestations of allergies. Bronchiectasis presents a different problem. Excluding those cases that occur early in life and are believed due to congenital weakness of the bronchial walls, bronchiectasis is believed to be the result of repeated and/or chronic respiratory infections. When recognized early and the infection arrested, the symptoms may be lessened, and the case may be controlled. When the bronchiectactic involvement is limited in area, such as one lower lobe, successful surgery (lobectomy, or partial lobectomy) will provide relief. As of the present, there is no accepted treatment for advanced generalized bronchiectasis.

There are many studies of bronchiectasis reported in the literature. Obviously, chronic infection of the nasal sinuses is not the only cause. Further, allergy has not been proven an etiological factor. But we otolaryngologists who study allergy know that allergic rhinitis—uncontrolled—predisposes a patient to comparatively mild subacute or chronic nasal sinus infection which may persist for long periods without the patient becoming alarmed. Quite properly, when patients do seek relief from bronchial disorders, they consult an internist. If the condition is sufficiently advanced to be recognized, and the internist is well-trained and sufficiently experienced, the diagnosis will be made promptly. An otolaryngologist should be

called into consultation. It is then the otolaryngologist's problem to arrest the infection; if allergic rhinitis is present, the otolaryngologist must recognize and make the diagnosis, and either treat the allergy or call an allergist into consultation.

But bronchiectasis provides an even greater challenge to the otolaryngologist, particularly he who is capable of treating allergic rhinitis. First, all sinus infection should be *entirely* cleared up. When the patient has an allergic rhinitis complicated with sinus infection, it is not enough to clear up that particular episode of infection; the allergic rhinitis should receive adequate treatment so that the patient will not be susceptible to recurrent nasal infections. Second, when I see the patient with nasal sinus infection with or without an underlying allergic rhinitis, but with definite bronchial symptoms, I refer the patient to a competent internist. By following these procedures, we will relieve some cases of bronchiectasis; more important, we will prevent the development of bronchiectasis in many more patients.

In summary, I wish to emphasize the logical conclusion that management of allergies will completely control only the uncomplicated cases of allergic rhinitis; complicated cases will require additional treatment, and will frequently require surgery. Surgery should not be considered until the allergic factors have been completely controlled and all reversible conditions have opportunity to return to normal. Then, if the patient is not relieved, and surgery is indicated, *the patient should not be denied the relief that surgery can give.*

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**THE CALCULUS OF PROBABILITY**

"One of the difficulties arising out of the subjective view of probability results from the *principle of insufficient reason.* This principle, the logical basis upon which the calculus of probability must rest according to the subjective view, holds that *if we are wholly ignorant of the different ways an event can occur and therefore have no reasonable ground for preference, it is as likely to occur one way as another.* Since first enunciated by James Bernoulli, this principle has been exhaustively analyzed by mathematicians. As the principle rests on ignorance, it would seem to follow that the calculus of probability was most effective when used by those who had an "equally balanced ignorance." However well men approximate to this ideal, philosophers and mathematicians hold themselves in higher esteem, and so the principle has fallen on lean days."—EDWARD KASNER and JAMES NEWMAN, Mathematics and the Imagination, New York, Simon and Schuster, 1940.

# THE USE OF IMPATIENS BIFLORA (JEWELWEED) IN THE TREATMENT OF RHUS DERMATITIS

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THE SCOPE of this communication is to report my own experiences with the use of *Impatiens biflora,* commonly known as jewelweed, in the treatment of poison ivy.

*I. biflora* or jewelweed is an old-fashioned galenic, which, when taken internally, acts as an emetic, cathartic and diuretic, though considered dangerous and therefore little used. The fresh juice is reputed to be efficacious in the treatment of rhus poisoning. The substance is a tincture made by maceration of *I. biflora,* representing 10 per cent dry drug strength and containing 54 per cent alcohol. The mechanism concerned in the action of this drug in the case of rhus dermatitis is not definitely established, although the results obtained following its use are dramatic and almost of specific nature. In my use of this agent in cases of rhus dermatitis, I dilute one part of the standard preparation with four parts of water and use the diluted mixture as a topical application to the affected skin.

The present study deals with a group of 115 patients afflicted with rhus dermatitis whom I had the opportunity to treat during the past fifteen years. All the patients in this series were seen during the acute stage of the disease, a very short time after their exposure to the weeds and the appearance of the skin eruption. The patients were divided into two main groups, namely, those that were treated with jewelweed alone and those that were treated partly with jewelweed and partly with other medications. Standard preparations of jewelweed in dilutions 1:4 were employed in all 115 patients. One group of thirty of the 115 patients had certain portions of the affected skin treated with a mixture of calamine lotion and 0.1 per cent menthol, and the rest of the lesion treated with the jewelweed preparation. Another group of thirty out of the 115 patients was partly treated with Burrow's solution in dilution 1:20, and partly with jewelweed. A third group of six patients was similarly treated with 0.5 per cent of hydrocortisone ointment applied locally to some portions of the involved skin and jewelweed applied to other parts.

The results obtained with these various drugs were compiled and evaluated, and may be briefly summarized as follows: 108 of the 115 patients treated with jewelweed preparations responded most dramatically to the topical application of this medication and were entirely relieved of their symptoms within two or three days after the institution of treatment. The remaining seven patients failed to respond to this form of

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therapy. The latter group was then treated with adrenocorticotropic hormone (ACTH) given parenterally or with corticosteroids given orally, with very good results. The results of treatment were not nearly as gratifying when the other therapeutic agents were employed. Thus, when calamine lotion, Burrow's solution, or local corticosteroids were applied to the skin lesions, only 50 per cent of these patients reacted favorably. However, treatment in these cases had to be extended over a period of a week or more before the condition subsided. The remaining 50 per cent of patients were not improved even after treatment for a week or more; these were then treated with jewelweed and then showed rapid improvement. The good results that were obtained with the use of jewelweed in the treatment of rhus dermatitis were so consistent and universal that I would like to say that this preparation is perhaps the safest and most efficacious in the control of this disease when hormonal therapy is contraindicated.

Because of the difficulties in drawing conclusions from clinical results alone, I have undertaken the following experiments upon myself. I reproduced the lesions caused by poison ivy on both of my arms. The skin lesions were made to appear in rows and a different medication was applied to each row. The drugs used consisted of jewelweed, calamine lotion with 0.1 per cent menthol, Burrow's solution in dilution 1:20, and local 0.5 per cent hydrocortisone ointment. The results of these experiments were quite conclusive and showed, as in the case of the clinical application of these drugs, that jewelweed was most effective in clearing the lesions in the shortest period of time. It was thus found that this therapeutic agent caused prompt disappearance of the dermatitis and relief of symptoms within two or three days of its application and was superior to the other drugs used in a similar way as in the clinical trials.

Jewelweed is an excellent substitute for ACTH and the corticosteroids in the treatment of poison ivy dermatitis. My experience and the experience of others[1] with the use of topical corticosteroids has been disappointing. In addition, the oily nature of the vehicle of this drug may cause spreading of the lesion rather than arresting it, and its application therefore, is of questionable value.[2]

## SUMMARY AND CONCLUSIONS

Studies of rhus dermatitis have been pursued clinically on 115 patients, and experimentally upon the author himself. Evidence is obtained that jewelweed is a very potent and safe therapeutic agent in the treatment of this condition.

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*Submitted June 14, 1957*

# INTRACTABLE ASTHMA CAUSED BY ASPIRATION OF A CORK FROM A NEBULIZER

## A Case Report

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THE FOLLOWING case is being reported because it represents an interesting complication in an individual who had suffered from bronchial asthma for many years.

### CASE REPORT

Mr. R. had had asthma since the age of twenty-eight, and was treated adequately for seventeen years until June, 1951, when he was fifty-one years old. He had used a nebulizer (Fig. 1) as required. In November, 1950, while using this

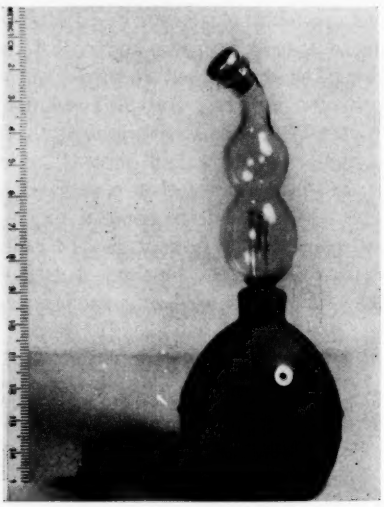

Fig. 1. Nebulizer used by patient.

nebulizer, he forgot to remove the cork and accidentally inhaled it. He said he coughed it out about eighteen days later. There was no apparent change in his general condition until June, 1951. Henceforth, his asthmatic control decreased and he became progressively weaker and more dyspneic. As a result, his activities

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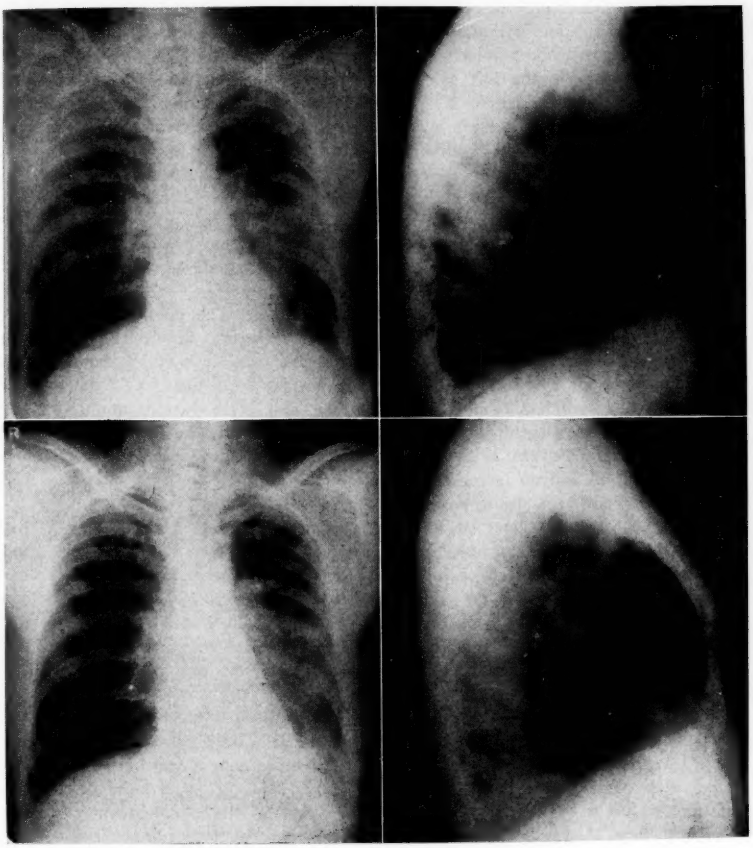

Figs. 2a and 2b *(above)* Chest roentgenogram taken February 2.
Figs. 3a and 3b *(below)* Repeat roentgenogram of chest taken February 9.

were sharply curtailed and by November, 1952, despite medication, he could not walk a block nor drive a car. In November, 1952, the patient's temperature was normal and the only relevant abnormalities were his emphysematous thoracic cage, and bilateral wheezing with a prolonged expiratory phase.

An attempt was made to have him avoid medication prior to skin testing, but he very shortly developed a severe state of asthma which required hospital care. At the hospital he responded well to antibiotics, antihistamines and bronchodilators, and was discharged after seven days. His initial white blood count was 12,800, with a differential showing 3 per cent eosinophilia. In his sputum, a 75 per cent eosinophilia was observed. The chest roentgenogram supported the diagnosis of emphysema and showed depressed leaves of the diaphragm, but fluoroscopic examination showed that the leaves of the diaphragm moved adequately. There was no evidence of an infiltrative lesion of the parenchyma of either lung.

Skin tests were positive for ragweeds, fungi, smuts, yeasts, kapok, goat hair, gum karaya, horse dander, hog hair, and several of the foods.

Upon his return home he relapsed. Despite the preparation of an allergen-free home, hyposensitization, symptomatic therapy and administration of antibiotics and steroids, there was no definite improvement. In January, 1953, he developed a sharp, severe pain in the left side of his chest, which increased in severity and frequency. Tryptar inhalations were initiated, and upon coughing up much sputum on the first day or so, he improved. However, the pain recurred, accompanied by a slight fever (100.2° F.). The pain became more severe over the precordium and radiated to the back. He developed chills and a severe headache.

He was hospitalized on February 1, 1953, at which time he had slight cyanosis of his fingers and toes. His temperature was 102° F. and his pulse 120. The trachea was in the midline. He had generalized expiratory wheezes bilaterally. The breath sounds were increased at the left base and there were expiratory and inspiratory coarse, bubbling rales in the left base.

Initially, because of the pain, the chest was taped. The chest roentgenogram of February 2 showed a faint area of increased density which was mainly in the posterior part of the left lower lobe (Figs. 2a and 2b). There was a small amount of fluid posteriorly. The tentative impression was that the patient had a pneumonia. He was treated symptomatically for his asthma, and given various antibiotics for his infectious process (penicillin, streptomycin, chloromycetin, and later polymyxin). The repeat roentgenogram of the chest on February 9, showed further progression of the infiltration and an increase in the amount of fluid (Figs. 3a and 3b). The sputum was reported as being positive for acid-fast bacilli.

A bronchoscopy was done on February 16, at which time it was believed that a tuberculous lymph node had eroded into the left lower lobe bronchus, and there was a tuberculous infection of the left lower lobe. The patient was then transferred to the isolation section and started on antituberculosis therapy. Another bronchoscopy was performed on February 18 and a "black tumor" was seen and biopsied. The pathology report indicated that the material was of vegetable origin. A bronchogram done on February 24 showed a complete obstruction of the left lower lobe bronchus.

As a result, a left lower lobe lobectomy was performed on February 25, 1953. The lobe was atelectatic. In the bronchus was found a hard, black cork measuring about 1.0 cm by 0.25 cm. The patient's postoperative course was uneventful, and he was discharged from the hospital on March 7, 1953. Thus, a lapse of twenty-nine months occurred before this patient was cured of his complication.

Subsequently, this patient has done well following the prescribed allergy treatment, except that he suffers from mild asthma when he has an upper respiratory infection or when the weather is very windy.

## DISCUSSION

Foreign bodies in the lower respiratory tract have been adequately discussed in the literature and at medical meetings. There is no need to review the admonitions given. However, in reviewing the literature and by personal inquiries, we have been unable thus far to find a similar case.

## SUMMARY

A case is reported of an atopic patient whose bronchial asthma had been adequately controlled for many years, but who developed a state of intractable asthma following the inhalation of the cork from his nebulizer. The intractable status was cured by removal of the involved bronchus and lobe containing the foreign body.

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**THE DRUG OF CHOICE**

"There are real advantages in choosing the best drug for the clinical problem at the outset of treatment. For the seriously ill patient, time may be precious, and, if the first choice is the best drug for the situation, that irretrievable commodity is not wasted. Some thing short of the best may provide incomplete relief, no relief at all, untoward effects, or disaster. The patient is likely to assume, and perhaps he also has the right to expect, that his physician will provide the optimum drug for his condition the first time he writes a prescription. It is understandable that, having endured a period of unsatisfactory treatment, the patient may be reluctant to continue with an obviously trial-and-error process. For his part, it is not feasible for the physician to plead that there is no other way of determining the best drug.

"A bad initial impression of a drug often leads to enduring and unshakable prejudice and causes the physician to avoid using it in situations in which it is eminently useful and safe. Nothing is more likely to lead to a bad first impression than ignorance of uses, limitations, and dangers, and, conversely, nothing is more likely to lead to appropriate first impressions of new drugs than the knowledge which enables the physician to select the best drug for the therapeutic target; that is to say, the drug of choice."—WALTER MODELL, M.D. (Editor), *Drugs of Choice, 1958-1959,* C. V. Mosby Company, 1958.

# CLINICAL EVALUATION OF BENACORTOL

## An Antihistamine-Steroid Mixture Useful in the Short-Term Treatment of Allergic Diseases

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ANTIHISTAMINES and adrenal corticosteroids have been found useful in drug therapy of allergic disorders. This report deals with the clinical evaluation of Benacortol®,* an antihistamine-steroid combination of Benadryl® (diphenhydramine hydrochloride) and Paracortol® (prednisolone). In addition to antihistaminic properties, diphenhydramine exerts definite atropine-like[1] and sedative[1,2,3] effects. Because of the sedative effect, diphenhydramine has been successfully substituted for barbiturates[4] and in the management of emotionally disturbed children.[5] This study was to determine the usefulness of the tranquilizing action in preventing emotional disturbances resulting from prednisolone as well as in treating the psychological component of asthma. Also to be noted was whether any synergism existed, thus allowing lower dosages of prednisolone to be used in alleviating allergic symptoms.

### METHOD

Ambulatory patients suffering from allergy of the conjunctiva, nose, lungs, and skin were chosen as listed in Table I. An attempt was made to discard those with obvious infection or to control this with antibiotics.

The dosage varied from two to eight capsules daily for one week. The majority of the patients received three to four capsules daily.

Evaluation was made in the cases of atopic eczema and conjunctival involvement by comparative Kodachrome pictures taken with a Coreco camera. Involvement of the nose was evaluated by inspection, noting nasal blockage and rhinorrhea, as well as the character of the nasal mucosa. The same investigator examined the nose before and at the end of one week of therapy. Pulmonary function was determined by recording the half-second timed vital capacity,[6,7] using a Collins Vitalometer, and by obtaining the Respiratory Index (R.I.) as described by Gross and by Simon[8,9]:

$$\text{R.I.} = \frac{\text{Vital Capacity (ml) plus breath-holding time (seconds).}}{100}$$

In some patients who were too young to be cooperative, the results of therapy were determined by auscultation.

*Benacortol®, as supplied by Parke, Davis and Company, contains 2.5 mgm Paracortol® (prednisolone) and 25 mgm of Benadryl® (diphenhydramine hydrochloride).

TABLE I. RESULTS OF THERAPY WITH BENACORTOL®

| Disorder | Satisfactory Results | Unsatisfactory Results | Total |
|---|---|---|---|
| Allergic rhinitis | 55 | 10 | 65 |
| Allergic conjunctivitis | 5 | 0 | 5 |
| Asthma | 18 | 4 | 22 |
| Allergic rhinitis and asthma | 56 | 4 | 60 |
| Urticaria | 2 | 2 | 4 |
| Erythema multiforme | 2 | 0 | 2 |
| Drug sensitivity | 1 | 0 | 1 |
| Eczema | 9 | 1 | 10 |
| "Id" reactions | 2 | 0 | 2 |
| Totals | 150 | 21 | 171 |

TABLE II. BENACORTOL® IN ASTHMA: PULMONARY FUNCTION CHANGES

| | Average R.I. Before Therapy | Average R.I. After Therapy | Average ½ Sec. V.C. Before Therapy | Average ½ Sec. V.C. After Therapy |
|---|---|---|---|---|
| Successful results (47 Cases) | 42 | 55 | 1004 cc. | 1334 cc. |
| Unsuccessful results (6 Cases) | 47 | 44 | 1183 cc. | 1050 cc. |

## RESULTS

The over-all results are shown in Table I. Of a total of 171 patients, 150 had satisfactory relief of symptoms. This is 87 per cent, a figure which compares satisfactorily with any drug therapy for allergic disorders.

Table II shows the results of pulmonary function studies in cases of asthma. The pulmonary function changes closely paralleled the clinical status of the patients. It was noted that allergic asthma responded more readily and to smaller doses than did intrinsic asthma. Most of the asthma treatment failures were intrinsic cases. The Respiratory Index (R.I.) prior to medication ranged from 13 to 97, with an average of 42. After therapy, the R.I. ranged from 25 to 118, with an average of 55.

Table III lists the side effects which were few in number and not serious. This may be related to the small dosages of drugs used. It is to be noted that nervousness decreased in ten instances.

Table IV reveals the response to prednisolone. In twenty-one cases, lower dosages of prednisolone were necessary to control symptoms than on previous occasions when prednisolone alone was used. In four instances, prednisolone dosage was judged inadequate, and the patient responded to higher dosages of prednisolone alone. The average total daily dose of diphenhydraminehydrochloride was 91 mgm and of prednisolone, 9.1 mgm.

## DISCUSSION

Since it was logical to hope that there might be a synergistic as well as additive effect between the anti-allergic and anti-inflammatory actions of a glucocorticoid and the action of an antihistaminic drug in the treatment of allergic and inflammatory conditions, one of the less toxic dehydrog-

TABLE III. SIDE EFFECTS IN 171 CASES

| Side Effect | Number of Patients |
|---|---|
| Drowsiness | 5 |
| Reddened cheeks | 1 |
| Depressed | 1 |
| Nervousness increased | 4 |
| Nervousness decreased | 10 |

TABLE IV. STEROID RESPONSE

| | Number of Cases |
|---|---|
| Less nervous than on prednisolone previously | 8 |
| Less prednisolone required than when on prednisolone alone previously | 21 |
| Prednisolone dosage inadequate | 4 |

enated analogues of hydrocortisone was tested in combinations with a standard antihistamine in various types of allergic manifestations. Results confirmed anticipations; both prednisolone and diphenhydramine were effective in smaller dosages than usual. This may account for the minimal amount of undesirable side effects.

The increased effectiveness may be due to a number of factors. It is likely that the different pharmacological actions affect the allergic reaction at different sites. The sedative effect of diphenhydramine is probably beneficial since it is well recognized that emotional factors can play a large role in allergic symptomatology. Whether the emotional factors are primary or secondary is of litttle importance. It is evident that simultaneous therapy of the physical and emotional aspects is the best type of medical treatment. Further, diphenhydramine is of importance in relieving the nervousness sometimes associated with prednisolone therapy.

Whether the atropine-like effect of diphenhydramine is of value cannot be determined. Oral parasympathetic blocking agents have not been consistently successful in therapy of allergies, in spite of occasional evidence of increased parasympathetic activity.

Antihistamine activity consists primarily of competing with histamine or H-substances at the end organ. Here the increased capillary permeability and resultant edema are partially prevented. Prednisolone therapy, on the other hand, produces an anti-allergic as well as a nonspecific anti-inflammatory effect. Synergism of effect with antihistamines and steroids was not noted by Brown[10] using cortisone and pyrilamine maleate. The results obtained in this study using diphenhydramine and prednisolone were best in patients with pollenosis and atopic eczema. Poorer results were noted in intrinsic asthma.

## SUMMARY

1. Benacortol® (diphenhydramine plus prednisolone) is an excellent therapeutic agent in a wide variety of allergic disorders.

2. Dosages necessary for effective symptomatic therapy are relatively small and side effects, minimal.

ADDENDUM

Since this paper was submitted for publication, thirty patients with fall hay fever have been treated with Benacortol®; twenty-seven had satisfactory results from therapy.

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**THE SURGEON AND THE LAW**

"Surgeons in general arose in alarm over the introduction of the idea of opening an uninfected knee joint. We were berated editorially and at medical society meetings for doing 'bizarre surgery that was so fraught with possibilities of disaster as to be wholly unjustifiable.' It was made clear to us that if a case of that sort were to get into court as was likely enough and probably soon, we could not have protection at the hands of the profession, a more serious matter than laymen can realize.

"Law does not permit a doctor to do anything that has not already been done previously by somebody else, except on risk of penalty. The surgeon who is advancing his profession with new work stands at all times over the muzzle of a loaded gun hoping that no lawyer will come along to pull the trigger.

"It is highly adventurous for any doctor to get near the periphery of our professional circle. Doctors 'hang together unless they believe that some particular one should hang separately.' "—ROBERT T. MORRIS, M.D., *Fifty Years A Surgeon*, New York, E. P. Dutton, 1955.

# AN INVESTIGATION INTO ENVIRONMENTAL INFLUENCES IN BRONCHIAL ASTHMA

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OBSERVATIONS were made of a large number of new immigrants, previously reported healthy, who, shortly after their arrival in Israel, began to suffer from bronchial asthma. Their state of health could not be attributed to living conditions, since other immigrant groups, living under similar conditions, were not affected.

GROUP I

We are concerned with approximately 124,000 Jews from Iraq who immigrated into Israel during 1951-52. The immigration was not selective. These immigrants arrived in entire families, and were of all age groups, all social classes and varying economic standing. For centuries they had lived as an exclusive group, mainly urban. Ninety thousand came from Baghdad alone. There they had lived comfortably. Those from Khurdistan, numbering about seven thousand, were accustomed to doing heavy physical labor. Fifteen thousand were quite poor. Intermarriage between cousins was common.

In Baghdad, the climate is hot and dry in summer, cold and dry in winter. During the summer most Baghdadians sleep in the open air, on the roofs. Wealthier people enjoy modern conveniences, such as, electric fans and air conditioners.

Medical authorities agreed that in Iraq, bronchial asthma did not constitute a problem of importance. Nevertheless, from personal experience with Iraqi asthmatics who visited Israel (then Palestine) every summer before 1948, I can affirm that bronchial asthma did occur there. Cases came from all social strata, some from high dignitaries of State. Their asthma did not differ essentially from the usual pattern in regard to hereditary predisposition, previous history, onset, and course of the disease.

Other allergic conditions, such as urticaria and the like, are normal in incidence. Often the Jewish population suffered from what they called "spring anemia"—favism.

Now, suddenly, "not a single family of these newcomers is devoid of a case or two of asthma or allergic rhinitis." (E. Somakh in the Letters of the International Correspondence Society of Allergists, Series XVI, page 118.)

Our investigations were concerned with: (1) geographical distribution of immigrants in Israel; (2) age groups; (3) period of residence in Israel prior to the onset of the disease; (4) case histories; (5) hereditary predisposition; and (6) clinical picture.

*Geographical Distribution.*—The newcomers from Iraq are to be found in the coastal plain, which has a very hot, damp summer; in the mountainous areas of Jerusalem and Galilee, where summers are hot and dry, winters, cool and wet; and in the subtropical regions of the Lake

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TABLE I. AGE OF ASTHMATIC IMMIGRANTS FROM IRAQ AND ASTHMATIC RESIDENTS IN GENERAL ISRAELI POPULATION

| Age | Asthmatic Immigrants from Iraq | | Asthmatic Residents in the General Population |
|---|---|---|---|
| | No. Cases | Percent Incidence | Percent |
| 0- 9 | — | — | 27.8 \| 42.4 |
| 10-19 | 8 | 9 | 14.6 \| |
| 20-29 | 48 | 49 \| 77.0 | 16.0 \| 37.3 |
| 30-39 | 27 | 28 \| | 21.3 \| |
| 40-49 | 7 | 7 | 11.1 |
| 50 and above | 7 | 7 | 9.2 |
| | 97 | 100.0 | 100.0 |

of Tiberias (Sea of Galilee). Reports of physicians from the various regions reveal a point of striking interest, namely, the remarkably low incidence of bronchial asthma in the hill regions and in Tiberias (which alone has about 4,000 Iraqi immigrants).

Moreover, the area of high incidence is not the entire coastal plain, but one particular area in the vicinity of Tel Aviv, Jaffa and Ramat Gan. In Migdal Ashkelon, on the coast, among 2,000 Iraqui Jews, only twelve cases of bronchial asthma were reported. This is below the normal incidence rate of 1 to 2 per cent among the general population.

Similarly, in Tirah, a Maabara (transit camp) near Haifa, where it is hot and humid and where there are numerous olive trees, among 13,500 immigrants, including 6,500 from Iraq, only thirty cases of allergic disease occurred. With one exception, all these patients were adults.

*Age Groups.*—As a rule, in the general Israeli population (see table) the group from birth to nine years of age is especially subject to the disease (27.8 per cent), whereas among immigrants from Iraq no cases occur in this age group. In the general population, 14.6 per cent are afflicted in the group from ten to nineteen years of age. In this age group, among Iraqi immigrants only 9 per cent are asthmatic. To summarize, in the general Israeli population, 42.4 per cent of all those asthmatic are in the group from birth to nineteen years of age. Among immigrants from Iraq, only 9 per cent of asthmatics are in this age group.

*Period of Residence in Israel Prior to Onset of Disease.*—Of ninety-seven patients examined, five had lived in Israel less than six months; thirty-two, from six to twelve months; thirty-nine from one to two years, and twenty-one, two years or more.

*Case Histories.*—Little reliance can be placed on a patient's assertion that he has never suffered from any allergic disease. A thorough investigation frequently fails to elicit information. Occasionally a patient admits having suffered from urticaria, but never from hay fever. Shortly before the onset of bronchial asthma, colds with and without high temperatures and cough, especially at night, are reported.

Not infrequently the sequelae to neurodermatitis preceded the asthma. We are familiar with this succession of symptoms in asthmatic children. To find it in adults is rare and interesting.

*Hereditary Predisposition.*—In spite of frequent intermarriage between cousins in Iraq, a hereditary dispostition was found in only 10 to 12 per cent whereas in other groups of asthmatics it is as high as 50 per cent. The onset of allergic diseases in patients with hereditary predisposition is earlier. Possibly the children in the group being free from asthma is an important consideration, and, in fact, here we are confronted by a typical form of "acquired allergy" (*sensu strictiori*, every allergic disease is acquired).

*Clinical Pictures.*—This differs little from the usual one of bronchial asthma. Eosinophilia was found in blood and secretions (sputum and nasal mucus). No other reason, save allergy, could be discovered to account for eosinophilia. The outstanding feature of the clinical picture is the psychic behavior of the patients. This will be discussed later.

Skin testing yielded consistent and enlightening results:

1. Of ninety-seven patients examined, only two showed positive reactions to food (fish and milk), but in both cases, food was not the only cause of the attacks.

2. Thirty-four patients showed reactions to bacterial allergens, especially the extracts from the patient's sputum.

3. Eleven patients showed reactions to pollen, but only in one case was there definite clinical pollen allergy (to Bermuda grass).

4. Sixty-five patients reacted to molds, especially to extracts from the patients' bedding, cotton, seagrass and feathers, rarely to straw. This is a very high rate of allergenization in a very short time. Apparently, sensitivity to fungi is readily acquired in a chronically-inflamed membrane of the air passages. Generally patients feel relieved immediately after a change of climate but this may be due to changing the "psychic milieu" as well, although there is proof that fungi cause the attacks.

Whatever the cause of the disease, the "way back," that is to say, the return to normal, is most difficult. Nevertheless, we know many cases where the disease is definitely under control.

*Discussion.*—Our observations may be summed up as follows: A considerable proportion of a group of immigrants from Iraq, previously reported healthy, developed bronchial asthma within a relatively brief period, whereas other immigrants, living under similar conditions, were free from asthma.

Our investigations showed:

1. Not all immigrants from Iraq were affected; the problem is not an ethnic one.

2. The immigrants became ill only in a geographically well-defined area (the neighbourhood of Tel Aviv).

3. Few allergic diseases were found in the families, in fact, in only 12 per cent, as compared to 50 per cent in the general population.

4. The case histories revealed few allergic diseases. Occasionally there had been urticaria. Asthmatic attacks were sometimes preceded by neurodermatitis or eczema, the typical juvenile form of allergy.

5. There is a totally different age composition:
   (a) No children below the age of ten are affected, as compared to 27.8 per cent among other asthmatics.
   (b) The majority of those affected are twenty to thirty years of age. Fifty per cent of all affected are twenty to forty years of age.
   (c) The illness is due mainly to bacterial allergens and fungi, rarely to food or pollen, the latter requiring a much longer time for sensitization.

Hence we conclude that the bronchial asthma under investigation is not of the usual hereditary type but rather an "acquired-grafted" allergic disease.

All the Iraqi immigrants experienced more or less the same changes as regards housing and diet and all faced similar psychological conflicts and economic difficulties, yet by no means did all react in the same way. Dr. Samuel Adatto, an elderly physician, who, prior to settling in Israel, had practiced in Baghdad for twenty-six years (1919-1945), offered the following explanation:

The distribution of immigrants from Iraq was not a matter of chance. As far as possible, those from mountainous districts (Kurdistan) were settled in the hill regions of Israel but a very large number of the poor remained in transit camps. The majority, about 90,000 from Baghdad, the largest city in Iraq, settled in and around Tel Aviv, the largest city in Israel, where they expected to find suitable living conditions. Psychologically, they were not prepared to be pioneers to the extent of changing their mode of life or their occupations. In particular, they were unwilling to undertake manual labor. These people were not rich enough to do nothing, nor were they poor enough to do everything.

Only a very small proportion could live as they had lived in Iraq. Although not poor, they had a struggle to adapt themselves to their new environment and to accustom themselves to the damp heat of the summer nights, so different from their climate in Baghdad. The most powerful factor in disturbing or hindering a cure is the sufferer's dissatisfaction with his circumstances. In such cases they offer no resistance but surrender to the disease.

The poor among these immigrants, especially those accustomed to manual labor, had little difficulty in finding employment and in adapting themselves to conditions. Indeed, they usually found better conditions than those to which they had been accustomed.

### GROUP II

In Group I, the appearance of bronchial asthma seems to be uncongenial environment. In Group II, a tremendous contrast appears. Existent asthma disappeared and no new cases were reported, even under the influence and extraordinary hardships of concentration camps.

In the course of the last seven or eight years, I have examined a number of patients suffering from bronchial asthma, all of whom related more or less the following history: For many years they had suffered from bronchial asthma, but during their confinement in a concentration camp they had no real attack. Such an attack, they declared, would have meant certain death. Comparatively soon after their rescue, sometimes within months, severe attacks recurred, exactly as before.

Not all asthmatics succeeded in overcoming their attacks in the camps. Many such people, unfit for work, were quickly exterminated. The question remains, "What enabled the others to survive in that environment of mortal dread, constant fear and pressure, bad housing, near starvation and unaccustomed physical work?"

Often, tension has the effect of keeping an asthmatic state in check for some time. A tennis champion, suffering from hay fever in springtime, could play a whole set in the open air but, as soon as he put away his racquet, he started sneezing.

Another patient had a severe attack of asthma in Haifa but instead of going to a doctor for an injection, drove back in his own car, practically non-stop over 100 km. On arrival in Jerusalem he could not get out of his car and had to be given an injection as he sat behind the wheel.

In these cases the tension lasted for hours, even days, but what happens when it continues for months and years?

Dr. Lucie Adelsberger, formerly of the Robert Koch Institute in Berlin where she was a leader in experimental allergy, and now at the Montefiore Hospital, New York, was herself an inmate of the Auschwitz Concentration Camp. She replied in detail to my query. In brief, she reports that in the course of two years she saw only three patients suffering from allergy. One patient (female) suffered severely from asthma, one from urticaria and one from migraine. She expresses her own amazement that these internees in concentration camps should have lost their allergies, and suggests that the explanation of "psychic reaction" is unsatisfactory. She points out that such a state of starvation brought about immense changes, such as those of metabolism, nitrogen balance and low BMR. She suggests that these changes may have played a part.

## SUMMARY

*Group I.*—We have observed that a considerable proportion of a previously healthy group of immigrants came down with bronchial asthma within quite a short time (six months to two years), in contrast to other groups of immigrants who remained free from asthma under very much the same conditions. The disease did not affect the whole ethnic group, but only a part, in a geographically well-defined section of the country.

Whereas, clinically, the disease does not differ from the usual manifestations, including eosinophilia in blood and secretions (sputum), it is rather suggestive of the "acquired type" of asthma without a hereditary background. Family involvement was almost non-existent, in spite of frequent intermarriages. Excepting the juvenile forms of allergy (neurodermatitis), no previous allergic afflictions were reported.

The age group, twenty to thirty (-forty) was affected most. The young age groups, below ten, were almost exempt, while generally in our country the number of asthmatic children of this age is exceptionally high. The allergic condition was found to be limited to bacterial allergens and molds-fungi, with an almost complete lack of allergy to foods and pollen, the latter being known to require a prolonged period of sensitization.

A peculiar psychic attitude was observed, symbolizing an "escapism into disease" without any sign of active resistance against the maladv.

The particular conditions of the age groups which were affected most have been discussed.

*Group II.*—In contrast to this first group, a period of freedom from bronchial asthma for two or more years was reported by numerous concentration internees who had previously suffered from asthma. No recurrence of the illness was reported among the inmates.

NOTE: Now, some two years after completion of this paper, we find this special group I of immigrants almost completely integrated in the new conditions, and the phenomenon of "mass-malady" (Massenerkrankung) of asthma has come to a natural end.

New sufferers from asthma are less frequent. Their number and age composition correspond to those of the asthmatics among the general population.

We considered it necessary to record these interesting observations as a unique contribution to the importance of environmental influences on the genesis and course of bronchial asthma.

*Street of the Prophets, Hassidoff House*
*Submitted December 28, 1956*
*Resubmitted May 6, 1957*

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**THE AVERAGE MAN**

"The difficulty is serious and shipwreck certain. To show this in a model situation let us examine the mean of two spheres. The first has unit radius and we shall choose a scale such that surface area and volume are also unity. The second, I will suppose, has radius 3 and, necessarily, will have a surface area of 9 and volume 27. Means of 2, 5 and 14 are incompatible; a sphere of radius 2 would have a surface area 4 and volume 8 exactly; no concession is possible, a sphere can have no other shape. Men's shapes unfortunately can vary, and M. Quetelet profits therefrom. By combining the mean weight of 20,000 conscripts with their mean height, we should produce an absurdedly fat man and, whatever Reynolds might have said, a poor model for an artist. This eminent painter, in his Lectures on the Fine Arts preceded Quetelet in setting up the average man as the type of perfect beauty. If such were the case, suggested Sir John Herschel, ugliness would be the exception. I cannot follow his argument. The individual traits of perfect beauty would not be rare; indecorously jumbled together they would lack merit. Grace stems from harmony. Chance doubtless would summon few elect and, despite Sir John Herschel, in the ill assorted assembly, if ugliness formed the exception, the grotesque would become the rule.

In the body of the average man our Belgian author sets an average soul. To summarize the moral qualities it is necessary to cast 20,000 characters in one. The specimen man would be without passion or vice, not foolish, not wise, not ignorant, not knowledgeable, generally dozing, for it is the average between wakefulness and sleep; he would answer neither yes nor no, and be in all things mediocre. After remaining alive for thirty-eight years on the average ration of a healthy soldier, he would die, not of old age, but of an average disease which statistics would discover for him." (Lancelot Hogben, F.R.S., Statistical Theory, W. W. Norton & Company, Inc., New York.)

# Progress in Allergy

## ENZYMATIC MECHANISMS IN ALLERGY

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FOR MORE than half a century the allergy concept has been one of the leading ideas in biology and medicine. However, most of the problems it has raised still await solution. These problems are complex and manifold and they are linked with such fundamental questions as the response of living matter to its environment, the specificity of this response and the way it is influenced by the past history of the species and the individual. Since there is no doubt that ultimately all these questions have to be answered in chemical terms, progress has depended largely on the advance of biochemistry.

It is almost a platitude to assume that enzymes must play a role in allergic phenomena, since the rate of chemical processes in living matter is controlled by enzymes. However, when we come to a more specific statement of our problem and start inquiring into the precise role played by enzymes in allergy and the nature of the enzymes involved, we become aware of its difficulties and of the gaps in our knowledge. Although enzymatic hypotheses were formulated within the first few years of the history of allergy, hardly any of the earlier data can be considered valid by present-day standards.

Contemporary research in this field has just reached the stage when everything seems hopelessly confused. It is hard to imagine how truth and order can ever emerge out of the chaos of disconnected and contradictory observations. However, all scientific inquiries follow the same pattern: after the initial illusion of simplicity comes a bewildering maze of increasing complexity until suddenly everything appears clear and almost self-evident. It is the misfortune of the present reviewers to have to deal with the enzymatic problem of allergy at its chaotic stage, but this is the point at which a review is most needed.

Practically all research concerning enzymatic phenomena in allergy deals with the *allergic response,* that is the final phase of the whole chain of events of the allergic phenomenon. This leaves out such important problems as the allergic terrain, factors of sensitization and the mechanism of antibody formation. The interesting "immuno-catalysis" theory by which Sevag explains antibody formation has been adequately dealt with in his monograph[240] and in a recent paper in this Journal[241] and will not be considered here.

The allergic response is the sum of the reactions elicited in a sensitive individual by the antigen or an equivalent allergic stimulus. It can be represented by the following sequence: allergic stimulus → antibody → sensitive cell → mediator → responsive cell.[44] In this scheme, antibody may be unnecessary (as in physical allergy and the so-called anaphylactoid phenomena) and the sensitive cell may be identical with the responsive cell.

An allergic stimulus may be defined as a stimulus to which only a minority of sensitive individuals respond. Its distinctive character becomes clearer when it is compared with the non-allergic or pharmacological stimulus. The response to a pharmacological stimulus depends essentially on the nature of the stimulus. Morphine, for example, elicits qualitatively the same response in all individuals and this response is specific for the drug. The allergic response, on the other hand, is determined qualitatively and quantitatively by the individual pecularities of the subject. Instead of a pharmacological specificity, it has immunological specificity.

Each pharmacological stimulus has its own specific mechanism of action but there is reason to believe that the various types of allergic responses are elicited by some common mechanism. Much of the work done on enzymatic phenomena has been part of a quest for a unitary hypothesis in which a central enzymatic reaction supplies a common basic mechanism for all allergic responses.

Apart from a brief recent survey published in this Journal,[28] no comprehensive review has appeared on the enzymatic problem of allergy. It has however, been treated more or less exhaustively in reviews of a more general nature[16,27,47,113,195,232,261] or dealing with related problems.[196, 198,199,213,260,263,282]

## ENZYMATIC CONCEPT OF THE ALLERGIC RESPONSE

One of the earliest explanations of anaphylaxis was based on the assumption of an enzymatic process taking place in the serum of the sensitive animal treated with the antigen. A brief recapitulation of the evolution of ideas will no doubt help to set the contemporary work against its proper background. A more detailed discussion of early literature is to be found in Wells[290] and Zinsser.[303]

In 1907, Richet observed symptoms of anaphylaxis when a mixture of antigen and sensitized dog serum was injected into non-sensitized dogs.[208a] This fact was interpreted as the formation of a toxic material called *apotoxin* by the action of the antigen on a hypothetical precursor, *toxogenin*. Richet's results were confirmed and extended by Friedberger who gave the name *anaphylatoxin* to the toxic product formed by the interaction of antigen, antibody and presumably complement.[64] Using the concept of "parenteral digestion," developed by Vaughan,[279] Friedberger made the following hypothesis: the injection of an antigen into an animal is followed by the formation of specific antibodies; when the antigen is reinjected, these antibodies, together with complement, act as enzymes and tend to break down the antigen. This results in the formation of toxic products which constitute anaphylatoxin. This early anaphylatoxin theory was linked with Abderhalden's "Abwehrfermente" which were claimed to be specific enzymes produced in the body after injection of foreign substances and which are capable of destroying these.[1]

The original anaphylatoxin theory was easy to disprove. It became obvious that the infinitesimal amounts of antigen adequate to elicit lethal anaphylactic shock could not provide a sufficient amount of protein split products to account for the toxic effects.[284] Friedberger's interpretation also lost ground when it was shown that toxic properties could appear in guinea-pig serum treated with such non-specific and non-protein substances as kaolin, agar, and starch.[25,188,189]

The most decisive blow to the anaphylatoxin theory was delivered by Dale.[38] His findings, together with those of Schultz,[237] Weil[284] and others

indicated that isolated smooth muscle, taken from sensitized animals and carefully washed free of plasma, still responded to the specific antigen. As a result of the ensuing controversy, the emphasis was definitely shifted from the humoral to the cellular aspects of the anaphylactic reaction.

For some reason, not entirely clear today, the enzymatic mechanism was closely linked with the anaphylatoxin theory. Under the weight of the arguments in favor of the cellular theory, research on enzymatic processes in allergy all but stopped for about twenty years.

It has been known since the end of the last century that the serum or plasma of most animals possesses proteolytic activity[42] and also, paradoxically, the ability to inhibit the action of trypsin and other proteases.[106] The only enzymatic theory which survived the crisis of the 'twenties was based on the assumption that in normal blood the protease and its inhibitor are linked together in a loose combination. As a result of the antigen-antibody reaction the enzyme-inhibitor complex is dissociated and the protease is set free. The action of the protease is not directed against the antigen any more; it attacks the proteins of the host.[26,117]

Revival of the enzymatic hypothesis of allergy was stimulated by significant advances in the knowledge of blood proteases.[30,31] It was discovered that the principal proteolytic enzyme of plasma, variously called serum trypsin, serum tryptase, fibrinolysin or plasmin, is formed by the activation of an inactive precursor, profibrinolysin or plasminogen. Inactivation of this enzyme by serum inhibitors is an irreversible process and does not result in the formation of a reversible enzyme-inhibitor complex. Evidence was also produced that plasmin is different from the digestive proteases and does not represent the overflow of the pancreatic production of trypsin or chymotrypsin into circulating blood. The plasminogen-plasmin system will be discussed in more detail below, together with other enzyme systems which may take part in allergic processes.

The strongest impetus to explain allergy in enzymatic terms was probably given by the work of Rocha e Silva who was able to produce anaphylactoid phenomena by injections of trypsin.[210a,213,215] He and his associates also confirmed Nolf's[187] observations on increased fibrinolysis during anaphylactic and anaphylactoid shock.[216,219,221,238] Other workers made similar observations in traumatic and surgical shock and under different conditions of stress.[120,254]

It might be useful, at this point, to clarify the somewhat confused terminology employed in reporting the results which will be surveyed in the following section. Fibrinolysis, that is the spontaneous dissolution of blood clots, was first described by Dastre in 1893[42] and observed by Nolf[187] in conditions related to allergy. Since the discovery of plasmin, fibrinolysis has been interpreted as the result of proteolysis. Fibrin or fibrinogen were used as substrates by most workers who studied proteolysis in the allergic reaction and who consequently, referred to the enzyme as fibrinolysin or plasmin. In most of these investigations, no evidence was produced that the enzymatic actions described were in fact due to the protease plasmin. The use of fibrinogen or fibrin as a substrate presents the advantage of an incomparable sensitivity[119] but also introduces errors which have contributed to the present confusion. These points will be examined below in more detail. In the mean time, the terms protolytic enzyme or protease will be used unless the writer produced some evidence of specificity. These terms designate all enzymes capable of hydrolyzing peptide bonds. Distinction is made between proteinases and peptidases

(or, in Bergmann's nomenclature, endopeptidases and exopeptidases)[22]: the first break down large protein molecules in smaller fragments while the latter can only attack terminal peptide linkages. Further differentiations, according to substrate specificity, optimum pH, etc., will be mentioned with each enzyme.

It has been discovered in recent years that most proteases can also hydrolyze ester linkages.[183a] Synthetic amino acid esters, which are convenient substrates for many proteases, are in widespread use.

Another point to be mentioned here concerns the chemical transmission of the allergic response. The histamine theory has introduced us to the idea that allergic manifestations are not caused directly by the antigen-antibody reaction but are mediated by the release of some chemical agent of endogenous origin. The best known of these, of course, is histamine but many workers have felt that there is room for other substances in the pathogenesis of many allergic symptoms. Besides the recently discovered role of 5-hydroxytryptamine (serotonin) in allergy, there are a number of peptides (bradykinin, kallidin, leukotaxin, et cetera) which may also be mediators.[167] In German literature, these substances are designated by the generic term of "sekundäre Reizstoffe."[294] In this review they will be designated as *mediators* and the inactive or bound forms from which they may be generated will be called *promediators.*

## EVIDENCE FOR ENZYMATIC MECHANISM

Two types of evidence have been presented in favor of the enzymatic hypothesis: the appearance of enzyme activity as a result of allergic stimulation and the production of allergic-type manifestations by means of enzymes.

1. *Enzymatic Activity Associated with the Allergic Response.*—This has been observed *in vitro* in isolated tissue preparations, in the serum or plasma of sensitized animals and also *in vivo* in body fluids and tissues of animals injected with the homologous antigen or with an anaphylactoid agent. Enzymatic action was demonstrated in most experiments by incubating tissue, serum or their extracts with the appropriate substrate. In a number of investigations, enzymatic effect was shown indirectly by an increased breakdown of proteins in the tissue.

(a) *Proteolysis in isolated tissues or cells.*—In view of the essentially cellular nature of anaphylaxis, it was logical to investigate whether addition of the homologous antigen to tissue fragments taken from sensitized animals would give rise to some demonstrable enzyme activity. Ungar and Parrot showed in 1936[274] that guinea-pig tissue slices would react to the addition of antigen by release of histamine. In 1947,[259] this same technique was used for the demonstration of proteolytic action. Lung, liver and kidney slices, taken from guinea-pigs sensitized to egg albumin, were added with the antigen and incubated with fibrinogen. The degree of proteolysis was evaluated in terms of the breakdown of fibrinogen to the point where it becomes non-clottable by thrombin. The results of the experiments indicated that addition of the antigen results in protease activity. No such activity was observed when egg albumin was added to non-sensitized guinea-pig tissues. When tissue slices were treated with peptone a similar and even more marked proteolytic effect was observed.

In 1949, Herberts obtained similar results with lung extracts.[100] These extracts, however, were obtained with low speed and short time centrifu-

gation and probably contained intact cells. After addition of rather high concentrations of antigen, proteolysis was measured by determination of free amino nitrogen by the Van Slyke method. The protease responsible for this action is activated by cysteine and manganese. Its optimum pH is around 5 to 5.5 but the enzyme is still active in the physiological range. Herberts believes that tissues contain an inhibitory factor, destroyed at 60° C. More will be said of Herberts' results when we deal with *in vivo* proteolysis.

In 1955, Ungar and Damgaard[268] used guinea-pig tissue slices to which homologous antigen or anaphylactoid agents were added *in vitro* and proteolysis measured without addition of extraneous substrate. Samples of the suspending fluid were precipitated with trichloracetic acid and the filtrates read at 280 mμ for protein breakdown products. Previous results on increased protein breakdown were confirmed and a few additional observations were made. It was shown that proteolysis produced by antigen-antibody reaction or anaphylactoid stimuli was inhibited by soy bean trypsin inhibitor and sodium salicylate. Cell integrity appeared to be necessary for the reaction to take place: it was decreased in homogenates and completely abolished in cell-free extracts. Simultaneously with the estimation of proteolysis, histamine and heparin breakdown were measured. The two series of phenomena were quantitatively correlated. When fibrinolysin (bovine plasmin) was added to lung slices, it proved a comparatively poor histamine liberator. It was therefore concluded that fibrinolysin is probably not the enzyme activated under the conditions of these experiments.

Other experiments were done in perfused guinea-pig lung. During the first five minutes, histamine release and protein breakdown followed a parallel course. With longer periods, however, histamine release stopped while proteolysis continued for at least fifteen minutes. The most important observation made was that both protein breakdown and histamine are increased over ten-fold if a small amount of fresh guinea-pig serum is added to the perfusion fluid together with the antigen. This problem will be discussed in further detail below.

At the same time, Hayashi and his associates[91,92,256] were able to demonstrate the appearance of a proteolytic factor in a culture of tissue monocytes taken from rabbits sensitized to bovine serum albumin (Cohn fraction V). This antigen was used because it contains no protease or precursor of protease. The cells were grown in special culture chambers which allow a parallel study of the morphology and biochemistry of the cells. While the cells are observed under a phase contrast microscope, antigen can be added to the medium and samples of the medium can be collected without damage to the cells. If so desired, fluid can be continuously flowing through the chamber without interfering with microscopical observations. Results of these observations will be mentioned below.

After addition of the antigen to the culture medium, samples were taken at ten, twenty, thirty and sixty minute intervals and tested on fibrin clots. Activity of the enzyme was expressed in terms of the time necessary for complete lysis of the clot. Active protease was found in the chamber fluid collected ten minutes after addition of the antigen and did not increase in later samples, indicating that activation is produced within a few minutes after the antigen-antibody reaction takes place. Heterologous antigen (egg albumin added to bovine albumin sensitized cells) had no effect. The optimum pH of the enzyme is about 7.5. The enzyme is inhibited by ovomucoid which is known to contain a protease inhibitor. It is also inhibited

by the SH inhibitor *p*-chloromercuribenzoic acid and can be reactivated by an excess of cysteine sufficient to displace the inhibitor. The enzyme released from isolated monocytes is therefore different from both trypsin and plasmin which are not affected by SH inhibitors. At a later stage, an endogenous inhibitor appears in the culture fluid.

More recently, Sakakura and Hayashi (unpublished experiments) have observed the release of a similar enzyme from isolated skin from sensitized rabbits. The antigen was added to the skin slices suspended in potassium chloride solution. Samples of the suspending medium were tested on casein hydrolysis. Their activity was also inhibited by SH inhibitors and restored by cysteine.

It has been known that an allergic response can be elicited by addition of the antigen to the whole blood in rabbits,[121,46,73] guinea pigs[258] and men.[122] The reaction is detected by the release of histamine or more recently, of 5-hydroxytryptamine from the cells into the plasma. Humphrey and Jaques have shown that the addition of homologous antigen to a rabbit platelet preparation suspended in plasma released histamine and 5-hydroxytryptamine from the platelets and that this release is correlated with protease activity of the plasma.[112] The same correlation was also found in the case of spontaneous proteolytic activity of plasma. Hyperimmune bloods which had an unusually high protease-inhibitor content were refractory and did not release histamine on addition of antigen. Release of mediators did not take place in washed platelets suspended in Tyrode solution without plasma. Proteolytic activity was measured by using denatured hemoglobin or casein as substrates. In spite of these admittedly unsatisfactory substrates, proteolysis could be demonstrated in a large proportion of experiments. The antigen used in these experiments was type III pneumococcus polysaccharide. Such anaphylactoid stimuli as agar also caused activation of protease. An interesting observation made by these workers concerns the role of calcium ions in protease activation. They found that the presence of oxalate, citrate or ethylenediamine tetraacetate prevented protease activation as well as release of histamine and 5-hydroxytryptamine.

McIntire and his co-workers also used rabbit blood for studying histamine release.[153-156] Their conclusions are in contradiction with those of the workers mentioned above. They deny any connection between proteolysis and histamine release or any allergic response in general. Their negative conclusions are based on the following evidence: (a) Bovine plasmin is a poor and inconsistent histamine liberator in rabbit blood. This was noted also by other workers.[214,217,268] (b) Although soy bean trypsin inhibitor and bovine serum antitrypsin prevent histamine release by trypsin, they fail to do so in the case of antigen-antibody reaction. (c) Streptokinase fails to release histamine from rabbit blood *in vitro*. These points seem to indicate that, in rabbit blood, the protease activated by antigen-antibody reaction is different from plasmin. They also confirm the fact that streptokinase does not activate serum protease in rabbits.

(b) *Proteolysis in cell-free plasma or serum.*—As seen previously, the early theories of anaphylaxis postulated the appearance of proteolytic activity in the serum of sensitized animals treated with the homologous antigen. That such protease activation might actually take place in the absence of cells, was first shown in 1949.[273] In order to demonstrate proteolysis in serum, two conditions had to be fulfilled: a sensitive method had to be found which could detect low degrees of proteolysis and the

effect of the protease inhibitor present in serum had to be eliminated. The following experimental procedure was adopted: Serum from sensitized guinea-pigs was mixed with the antigen (egg albumin) and contact maintained for three minutes. After this interval, the euglobulin fraction was precipitated out by dilution and adjustment of the pH to 5.4. This left the inhibitor in the supernatant, while the protease, contained in the precipitate, was redissolved again and incubated with fibrinogen. Enzyme activity was estimated by clotting the remaining fibrinogen with thrombin. This method proved sensitive enough to demonstrate the activation of a protease in serum under the influence of the antigen-antibody reaction and by various anaphylactoid agents such as peptone and some high molecular polysaccharides (agar, bacterial polysaccharides, hyaluronic and chondroitinsulfuric acids). It was found important to add the activating agent to whole serum, not to the euglobulin precipitate. This indicated that isoelectric precipitation eliminated some serum factor essential for activation. This factor was also destroyed by heating to 56° C. for thirty minutes.

Some of these observations were confirmed in rabbit serum by Geiger[66] who also used fibrinogen as a substrate but used trichloracetic acid to precipitate the remaining proteins. Proteolysis was estimated in the filtrate by means of the Folin-Ciocalteu reagent. In some of these experiments, protease inhibitor was destroyed by treatment with chloroform which seemed to facilitate the demonstration of protease activation. Geiger used several antigens: bovine and porcine fractions II and V, sheep erythrocytes and plant proteins. The best results were obtained with sheep cells. It was also confirmed that non-sensitized sera as well as sera treated with heterologous antigen do not show activation. Mucopolysaccharides did not activate rabbit serum but their effect on guinea-pig serum was confirmed. Geiger was struck by the comparatively low degree of proteolysis observed in his experiments. This was probably due to the lack of sensitivity of his method.

The necessity to add the activating agent to whole serum to obtain activation was also confirmed by Geiger and indirectly by Euler and Heller[49-51] who published negative results after adding the antigen to the globulin fraction. Other negative results[114] are difficult to explain, unless by inadequate sensitization or, as suggested by Humphrey and Jaques,[112] by the use of an excess of phosphate buffer which reduced the concentration of calcium necessary for protease activation.

In 1953, Ungar and his associates[271] repeated their experiments with an improved technique for measuring proteolysis. In this method, after incubation of the enzyme with fibrinogen, thrombin was added to the mixture to clot the non-hydrolized substrate. After filtering, the amount of hydrolyzed material was measured by reading the filtrate in the ultraviolet spectrophotometer at 280 m$\mu$. By means of this method, protease activation was confirmed in the sera of guinea pigs sensitized to egg albumin or rabbit serum. Normal sera could be activated by a number of anaphylactoid agents and histamine liberators. The serum factor which was previously found essential for activation was further analyzed, especially in its possible relationship with complement. This part of the work will be discussed below together with other observations on the role of complement.

The latest work on protease activation of serum *in vitro* is that of Haining on the action of dextran sulfate on rabbit serum.[85] While both dextran and dextran sulfate release histamine from rabbit blood, dextran

fails to activate protease on addition to rabbit serum. With a high molecular dextran sulfate, however, Haining was able to demonstrate a high degree of activation which was paralleled by the histamine release when the agent was added to whole blood. Two interesting points emerge from Haining's observations. One, already mentioned by Ungar[271,273] and Geiger,[66] is that there is an optimum concentration for the antigen or the anaphylactoid agent for the production of protease activation. While 100 mg. of dextran sulfate produce a maximum effect on protease and histamine release, 500 mg. are practically ineffective. Another point is that serum activation may take place, as it occurred in his experiments with dextran, without the possibility of its demonstration by ordinary enzymological methods. This phenomenon, related to the mechanism of anaphylatoxin formation, will be examined in a further section.

(c) *Proteolysis produced in vivo.*—There is a considerable amount of evidence showing protease activation in the course of the allergic response elicited in the whole animal. Proteolytic activity was shown to develop in the blood, tissues and urine of animals injected with specific antigen or anaphylactoid agents. The first well documented observations were those of Rocha e Silva, Jaques and their associates.[215,216,219,221,238] They confirmed Nolf's earlier observations on fibrinolysis occurring in peptone shock in the dog.[187] By neutralizing with protamine the anticoagulant effect of heparin released during the shock, they were able to show that the clot formed dissolved in the test tube in a very short time. This was interpreted as a result of proteolytic activity appearing in the plasma after peptone administration. The same phenomenon was also observed in anaphylactic shock produced in dogs sensitized to horse serum.

These observations were confirmed under a number of different experimental conditions, in various species and by diverse methods.[32,101,130,132,137,186] Most of these experiments were done by direct observation of fibrinolysis in the blood of shocked animals or, by the action of serum on some protein substrate. One observation, although it produces only indirect evidence for protease activation, deserves a special mention because of its far reaching implications. In 1950, Beraldo[21] showed the appearance of bradykinin in the blood of dogs in anaphylactic and peptone shock. He was even able to produce bradykinin *in vitro* by adding peptone to dog plasma. It is known that bradykinin is the result of the enzymatic activation of a precursor, bradykininogen. This conversion may be operated by a specific protease, kallikrein, or by trypsin and even plasmin. Beraldo showed that bradykinin formation was inhibited by soy bean trypsin inhibitor and suggested that it resulted from the action of plasmin, itself released by the antigen-antibody reaction or peptone. This point will be further discussed in a later section.

Fibrinolysis was also studied in human blood, taken from allergic patients under the influence of the antigen. Lowell and his associates[148] gave intravenous injections of allergens to hay fever patients and produced fibrinolysis in a number of cases. The experimental results of Meyers and Burdon[168] are more difficult to interpret. These workers found that the total streptokinase-activatable plasminogen increased during acute asthmatic attack.

Fibrinolysis was also shown in human blood after administration of bacterial endotoxins (pyrogenic lipopolysaccharides extracted from Gram-negative bacteria). It has been shown by a number of workers that these extremely powerful anaphylactoid agents[283] produce protease activation in

the blood of rabbits, dogs and humans.[48,108,109,166] Westphal found a definite correlation between proteolysis and pyretogenic action.[294] It is usually assumed that these pyrogens act by releasing endogenous pyretogenic substances. The mechanism of this release may be related to the proteolysis induced by the endotoxines.

Damgaard and Ungar[39] have found that the urine of guinea pigs in which anaphylactic shock or Arthus phenomenon was elicited, hydrolyzed fibrinogen at a considerably increased rate. They interpreted this effect as due to the excretion of fibrinolysin, described previously by Macfarlane and Pilling.[151] More recently, however, it was shown that urine contains a kinase capable of converting plasminogen into plasmin.[9,79,297] When this urokinase is tested on fibrinogen, it activates the plasminogen present in the substrate as an impurity. By using casein as substrate, Ungar and Romano (unpublished experiments) could show that anaphylactic shock causes increased excretion of urokinase and not of a protease.

It appears, on the whole, that it is far easier to produce proteolysis *in vivo* than *in vitro* and it is probable that in most cases the enzyme originates not in the plasma but in the cells. There are a few experiments recorded in the literature where tissue protease activation was demonstrated after *in vivo* administration of the antigen.

In 1942, Oonishi[190] observed increased proteolysis in the lung of animals in which allergic pneumonia was produced. Similar observations were made by Herberts[100-103] in the lungs of guinea pigs in anaphylactic shock. Weimar[285] investigated the effect of peptone in frogs and found increased proteolysis in the liver of shocked frogs. Hayashi[91,92,] elicited an Arthus phenomenon in the skin of rabbits. At the height of the inflammatory reaction, he excised the skin, extracted it and prepared three fractions containing albumin, pseudoglobulin and euglobulin. The first two were inactive but the euglobulin fraction had a distinct proteolytic effect on fibrin. The same extract prepared from normal skin was inactive. Enzyme action detected in inflamed skin was abolished by heating the extract to 100 degrees C. and it was inhibited by ovomucoid and serum protease inhibitor. The skin protease detected in the Arthus phenomenon resembled the enzyme found by Hayashi in monocyte cultures in that it was inhibited by *p*-chloromercuribenzoic acid and reactivated by cysteine.

A further finding was that proteolytic action in the skin reaches its peak in about twenty-four hours. Two days later it had decreased and on the third day it had not only disappeared but the euglobulin fraction contained an inhibitor instead of a protease. Inhibitor content increases for several days and the euglobulin fraction collected during this period inhibits the effects of the fresh skin extract, the enzyme released from monocyte cultures and a commercial papain preparation. It has, however, no effect on trypsin or plasmin. In recent experiments, Matsuba and Hayashi (unpublished experiments) have observed inhibition of the Arthus phenomenon when the inhibitory globulin was injected together with the antigen or even some time after the antigen.

The observations just summarized leave little doubt that proteolytic phenomena do take place in many types of allergic reactions. This, however, does not necessarily mean that proteolysis is the cause of these reactions or even that it is in any way involved in their mechanism. The proteolytic reaction is far from being specific for the allergic response, and it has been observed in many types of injury and stress. The important point is discussed further in succeeding pages.

As may be judged from the preceding pages, proteases occupy a privileged place in the enzymatic concept of allergy. There are, however, a few references in the literature to other enzymes. At one time, Feldberg and Kellaway[55] suggested that histamine release might in some way be connected with the liberation of lecithinase. Certain snake venoms do certainly release both histamine and lecithinase and the latter effect is responsible for the hemolytic phenomena they produce. There is, however, no direct evidence that lecithinase plays a role in allergic processes. The venoms used in these experiments also contained proteases.

More recently, Havel and Boyle,[88] Worley and Lequire[298] and Inderbitzin[113] have observed the release of a lipoprotein lipase (also known as lipemia clearing factor) in the blood of dogs subjected to anaphylactic or peptone shock, as well as after injection of various high molecular carbohydrates. Since heparin is a cofactor of lipoprotein lipase, it is probable that there is some link between the release of both substances. Further experimental data will be necessary to understand the meaning of this phenomenon. For a discussion of this problem, see a review by Inderbitzin.[113]. Recently, the correlation between fibrinolysis and lipemia has received some attention.[11,77]

On the ground of their studies on oxygen requirement, temperature conditions, SH dependence, et cetera, of the cellular allergic response, Mongar and Schild[175a,176] have postulated the activation of a hypothetical enzyme which catalyzes reactions leading to histamine release and other effects of anaphylaxis. The important observations of these workers will be discussed in the section devoted to the cellular response.

2. *Production of Allergic Type Responses by Enzymes.*—There are many references in the older literature to the anaphylactoid effects of enzymes. The first clear-cut demonstration that a protease can produce all the symptoms of anaphylaxis was given in 1940 by Rocha e Silva.[210a] Since then, it has been shown that trypsin and papain release histamine from perfused guinea pig lung,[215] rabbit blood cells[153] and platelets.[112] Trypsin also produces shock in the frog.[286]

Curiously enough, plasmin, even at high concentrations, does not cause acute shock,[153,214,217] and, as was seen above, is an irregular and weak histamine liberator.[268] It was suggested by Yamura (personal communication) that species specificity is involved in the effect of plasmin; he was able to produce shock in guinea pigs with guinea pig plasmin but not with plasmin from other species. Johnson *et al*,[118] however, injected streptokinase into man without producing shock-like symptoms. Streptokinase would produce plasmin by activation of endogenous plasminogen. The results of these workers may be difficult to interpret because of the slowness of the injection. At the rate at which they injected streptokinase, trypsin would probably also have failed to produce an acute effect.

In other experiments, longer lasting effects of enzymes were observed either after single or multiple administrations. Rich and Duff,[208] in 1937, by injecting commercial or crystalline trypsin and crude papain into dogs produced definite hyaline or necrotic arteriolar lesions. Subcutaneous injection of a 5 per cent solution of crude trypsin resulted in the formation of subcutaneous nodules especially in rheumatic fever subjects.[171,234] Kellner and Robertson[125,126] gave single intravenous injections of varying doses of trypsin, papain, ficin, streptokinase and streptococcal proteinase to rabbits. The animals were sacrificed after intervals from a few hours to seven days after injection. A considerable proportion of

the animals developed myocardial damage similar to that seen in experimental serum sickness.[129,152] The only other tissue damaged was skeletal muscle. Similar observations were made in rats and mice. The least active of these enzymes producing carditis was trypsin, the most active was papain. Morimoto *et al*[177] have induced Aschoff-body-like lesions by injecting the endogenous protease produced in the Arthus phenomenon.

An interesting recent observation which also points to the role of proteases in allergy is the pruritogenic action of these enzymes. Arthur and Shelley[4,5] found that minute amounts of certain proteases injected intradermally caused itching, in the absence of any visible changes in the skin. This contrasts with the pruritogenic effect of histamine which is always accompanied by a visible wheal. Trypsin, chymotrypsin, plasmin, papain, and other plant proteases were shown to be pruritogenic. Pepsin, carboxypeptidase and leucine-aminopeptidase were inactive, together with a large number of various enzymes. The authors believe that pruritus is caused by direct action of the enzymes on the nerve endings and consider the endogenous proteinases as the chemical mediators of the itch sensation.[242] This, of course, implies that these proteinases would have to be activated by the various pruritogenic stimuli. Cormia[35] has shown that itching could be produced by streptokinase, plasminogen and by an epidermal protease.

The fact that certain types of allergic responses can be duplicated by enzymes answers to a certain extent the criticism raised against the enzymatic theory by Nakamura[128,182] who believes that protease activation is not the cause but the consequence of the allergic reaction. The facts just summarized still do not prove, however, that the enzymatic factor plays a decisive role in allergy. Protease activation may be just an incidental phenomenon without any pathogenic significance.

## CELLULAR RESPONSE AND ENZYMES

Even if one believes in the intervention of some humoral factors in the allergic response, as it is elicited in the whole animal or the allergic patient, there can be no doubt about the purely cellular nature of certain types of experimental allergic reactions. The best examples of this are the classical Schultz-Dale experiment and the responses observed in perfused organ preparations or in suspended tissue fragments.[233,274]

Hayashi and his associates[89,90,93,95,96] made morphological observations simultaneously with their enzyme studies reviewed in the preceding section. It was shown previously that tissue monocytes collected from the serous cavities of sensitized rabbits contain high concentrations of antibody.[70] In a pure culture of these cells, the basic morphological pattern of the antigen antibody reaction could be studied in detail under the phase contrast microscope. The cellular response to the antigen is entirely independent of the presence of extracellular antibodies; it can be elicited in carefully washed cells, resuspended in antibody-free fluid. On addition of the antigen, the first changes observed in the sensitized cells are the disappearance of cellular processes, marked swelling of the cytoplasm and formation of a fibrous network. This is the stage that corresponds to the release of protease. It is followed by some chemical change of certain granules which normally stain with neutral red and Janus green, but which after the antigen-antibody reaction, lose their affinity for the dyes. A third stage, starting about thirty minutes after addition of antigen, shows marked alterations: rod-shaped or filamentous mitochondria break

up into small granules and the Golgi bodies show varying degrees of deformation and degeneration.

In other experiments,[94] the antigen, bovine serum protein, was labeled with Congo red and injected into the skin of sensitized rabbits. Ten minutes after the injection, the macrophages were swollen and had taken up the antigen which stained the cytoplasm either diffusely or in the form of very fine granules. When the same labelled protein was injected into the skin of non-sensitized animals, the staining always occurred in discrete and fairly large granules. Similar results, obtained in cultured cells or after intraperitoneal injection of labelled antigens, show definitely that the antigen-antibody reaction takes place inside the cell and that protease activation occurs before gross cell injury is manifest. Monocytes and other tissue macrophages are the only cells in which an attempt has been made to correlate morphological and biochemical changes. In various forms of allergic reactions, however, other types of cells may play a similar role.[54,111,111a]

In 1953, Riley and West[209] and Graham and co-workers[74,75] discovered simultaneously a close correlation between histamine content and mast cell distribution. It has already been known that mast cells are rich in heparin. There is some indirect evidence suggesting that histamine and heparin may exist in mast cells as a complex.[78,157,227] Histological studies have shown that, under the influence of the synthetic histamine liberators, mast cells disintegrate and shed their granules simultaneously with the release of histamine.[208b] Similar observations were made with anaphylactoid agents, such as peptone and dextran. Under the influence of the antigen-antibody reaction, cell damage is less marked but the mast cells seem to lose their granules.[124,178,179]

There is a fairly widespread agreement on considering the mast cells as the main source not only of histamine and heparin, but also of 5-hydroxytryptamine.[193,208b,225,228,293] The importance of these cells in allergy, therefore, has gained further support by some recent findings concerning the role of 5-hydroxytryptamine, in the anaphylactic and anaphylactoid reactions of the rat, the mouse and, in part at least, the rabbit.[57,139,228,280,281,288]

On the ground of these observations, Weiser[287] has attempted recently to represent the whole of the allergic response as a mast cell reaction. Allergy would be primarily damage to the mast cells causing a release of the mediators which would act at a distance on other reactive structures. Becker[16] compares anaphylactic shock to the hemolytic system: the antigen plays the role of specific lysin for mast cells, probably with the help of complement. Such a generalization may not be borne out by the facts, since probably neither histamine nor 5-hydroxytryptamine are located exclusively in mast cells. As mentioned above, both mediators can also be released from platelets. There is no direct evidence either that isolated mast cells from sensitized animals would react *in vitro* with the homologous antigen. The nearest approach to such an experiment is the release of granules from mast cells of the rat mesentery by antigen.[178,179] We still need clear-cut experiments, showing that isolated mast cells, taken from sensitized animals, respond to the homologous antigen, with or without the presence of complement. It may be noted that Benditt[20] observed in rat mast cells the presence of a chymotrypsin-like enzyme.

Evidence is not lacking to show that isolated tissue slices, washed free of plasma, can respond to antigen as well as to anaphylactoid agents. Observations on the proteolytic component of this reaction have been

summarized above. In recent years, Mongar and Schild[174-176] have investigated some of the conditions of the allergic response in isolated tissue slices, especially the guinea-pig lung. They confirmed previous observations on the impossibility to release histamine by the antigen-antibody reaction from isolated intracellular particles, while synthetic histamine liberators are just as effective on these as on the whole cell.[34,80] It was shown that the proteolytic reaction also requires the intact cell.[268]

Mongar and Schild also confirmed the observation made by Parrot[194] in 1942 that the cellular response to the antigen does not take place in the absence of oxygen. They found, furthermore, that the response is inhibited by a number of metabolic poisons: cyanide, iodoacetate, *p*-chloromercuribenzoic acid and to a lesser extent by fluoride, azide and dinitrophenol. The allergic reaction is also limited by temperature: it can only be elicted between about 20° and 42° C. Synthetic histamine liberators behave very differently: their effect seems to increase by oxygen lack and cyanide and it augments with temperatures well above 42 ° C.

Further observations of Mongar and Schild also indicate that the cellular allergic reaction requires calcium and is completely abolished by the chelating agent ethylenediamine tetraacetic acid. Calcium dependence was also shown for histamine release from rabbit blood.[112,153a]

Response to the homologous antigen can only by elicited between certain pH limits: the optimum pH is around 7.4-7.6 and no reaction is observed below 6.5 and above 8.5.[176]

All these experimental results are interpreted by the authors as indicating an enzymatic mechanism of indeterminate nature. "Combination of antigen with antibody results in the activation of an enzyme system which catalyses reactions leading to histamine release and other effects of anaphylaxis. The activated enzyme is short-lived and in the normal course of events becomes rapidly inactivated."[175a]

The observations certainly indicate that histamine release by the cell under the influence of the antigen-antibody reaction is an active process. It is strongly reminiscent of the process of cellular excitation which is also inhibited by lack of oxygen, by the same metabolic inhibitors and by acid or alkaline pH. There are also a few observations suggesting that the cell loses potassium during the allergic response, as in excitation.[86,158] Unpublished observations by Matsuoka and Hayashi suggest that the sensitized cell submitted to the antigen takes up sodium. Sodium uptake is also a sign of cellular excitation.

A recent interesting finding by Goth and his co-workers[72] points to a further condition of the allergic response. These workers noticed that the anaphylactoid response caused by egg white or dextran is abolished in alloxan-diabetic rats and can be restored by administration of insulin. It had already been shown that insulin sensitizes rats to the effect of dextran.[2] It is interesting to correlate these facts with certain actions of insulin on the cell: it increases the penetration of sugars,[249] and diminishes the loss of potassium and entry of sodium.[36] This action on the two key ions of cellular excitation causes a rise in the resting potential.[301]

It appears from the observations just summarized that the allergic response of the cell is a form of excitation. It is an active process which can only take place in the structurally intact cell with normal metabolic functions capable of maintaining its excitability.

## ANAPHYLATOXIN, COMPLEMENT AND OTHER HUMORAL FACTORS

It is fairly well established that the antigen-antibody reaction, or the equivalent anaphylactoid stimulus can elicit a response in serum or other cell-free, protein-containing body fluids. Proteolytic aspects of this humoral allergic response have been reviewed above. An attempt will be made in this section to discuss the various problems of humoral allergy in terms of enzymatic mechanisms.

The term anaphylatoxin, created by Friedberger,[64] has been used with various meanings and was even applied to histamine[45] and other mediators. To conserve its original meaning, the name anaphylatoxin should be applied exclusively to material formed in cell-free plasma or serum by the antigen-antibody reaction. When it is injected into normal animals or applied to *in vitro* tissue preparations it should be able to reproduce the characteristic features of the allergic response. According to the terminology initiated by Bordet,[25] the similar material formed under the influence of peptone, agar, starch and other anaphylactoid agents, mostly high molecular carbohydrates, should be designated as "serotoxin." In present-day usage, there seems to be a regrettable confusion on this point and the term anaphylatoxin is used indiscriminately. It is almost always applied to toxic substances formed by the action of polysaccharides mixed with plasma or serum.

In 1950, Hahn and Oberdorf[84] resumed the study of serotoxins and found that guinea-pig serum treated with inulin, when reinjected into guinea-pigs, produced an anaphylactoid shock which could be prevented by antihistaminic agents. Hahn[81] showed later that this "anaphylatoxin" did, in fact, release histamine in the animals. Rocha e Silva and his associates [211,214,217,220,224] confirmed these observations and found that the best preparations to test anaphylatoxins were the isolated guinea-pig uterus or ileum and the perfused guinea-pig lung. On the latter preparation it was found that anaphylatoxins release larger amounts of histamine than the regular antigen-antibody reaction.

From the investigations of these two groups of workers a series of facts emerge. "Anaphylatoxin" can be best characterized by its ability to release histamine on injection into guinea-pigs or application to isolated organs. Formation of the material is inhibited by citrate, ethylenediamine tetraacetate and other chelating agents, although it can take place in the absence of either calcium or magnesium. Activation is also inhibited by heparin but heparin added after activation has no influence on the action of anaphylatoxin. Activation takes place only between pH 6 and 9. Anaphylatoxin formation is a chemical reaction taking place at a measurable rate which can be decreased by lowering the temperature. It seems to require free SH groups, since it is inhibited by zinc and *p*-chloromercuribenzoic acid.[68,81,83,180] The action of zinc is not specific for SH groups. It also inhibits plasmin which is not an SH enzyme.[71]

The precursor of anaphylatoxin has been carefully studied.[69,82] Serum heated previously to 60° C. for one hour loses its ability to being activated, although anaphylatoxin itself is heat stable. Ammonium sulfate at 2/3 saturation precipitates anaphylatoxin as well as its precursor. Using the Cohn method of fractionation, Hahn found the precursor material in fraction I-III. It seems, however, that material contained in two different subfractions is necessary for activation. Part of this material is in fraction III-0, part is in fraction I-III-1, 2, 3. The first factor is thermolabile, the second resistent to heat. Activation which occurs when the two factors

are mixed is accompanied by a shift of proteins from I-III-1, 2, 3 to III-0.

According to Hahn, it is unlikely that anaphylatoxin formation requires the presence of whole complement. Ammonia-treated serum in which C'4 has been inactivated can still be activated, although the activity will be diminished by 50 per cent. Treatment of serum with Congo red (which inactivates complement), does not prevent anaphylatoxin activation.

Hahn does not believe that anaphylatoxin formation is an enzymatic process, in spite of its temperature coefficient, its pH curve and its SH dependence. Rocha e Silva, on the other hand, is in favor of an enzymatic and presumably proteolytic mechanism, although he could not observe any protease activity with anaphylatoxin. As he admits himself, this does not mean that anaphylatoxin could not be formed by proteolysis of a transient nature which could not be detected any more when the activation is completed. As mentioned above, Ungar and Mist[273] and Geiger[66] observed short-lived protease activation by the same polysaccharides which are able to form serotoxins. Taking into account the enzymatic activity resulting from this activation and its short duration, it seemed unlikely that the protease itself could function as anaphylatoxin. It was suggested that this property was more likely to belong to the hypothetical protease activator which was tentatively called serokinase. This could bring about activation of cell proteases and thus produce the characteristic effects of serotoxin.[261,273]

There are many observations indicating that normal serum contains precursors from which active material can be generated by various treatments. Practically all the active substances are either formed by enzymatic process, or are enzymes or enzyme activators themselves. Two highly active polypeptides, bradykinin[212,218] and kallidin,[291] exist in normal serum as their inactive precursors, bradykininogen and kallidinogen. As mentioned above, Beraldo has observed the appearance of bradykinin in blood during anaphylactic and peptone shock in dogs. Since it is known that bradykininogen is activated by proteases and is inhibited by soybean trypsin inhibitor, it is logical to assume that bradykinin formation has been preceded by protease activation. Activation of kallidinogen is also operated by a protease known by the name of kallikrein.[63] This enzyme, however, is so specific that it is not known to attack any other substrate besides kallidinogen. We may note here that both bradykinin and kallidin are destroyed by another protease, chymotrypsin and probably also by certain peptidases.

According to Lewis,[145] it seems likely that there are several proteolytic enzymes capable of splitting one of the plasma proteins, probably an $\alpha_2$-globulin, producing a group of closely related polypeptides, with powerful smoth muscle stimulating and vasodilator activity. For these substances, he proposed the generic name of "kinins." Several workers believe that bradykinin and kallidin, if not identical, are at least very closely related compounds; by their pharmacological properties, their chromatographic behavior and other tests applicable to incompletely purified material, the two substances are indistinguishable.[63,107,230,277,278] Enzyme specificities involved in their formation will be discussed below.

Another example of the formation of an active substance from serum *in vitro* is the permeability factor of Miles and his co-workers.[169,295,296] They found that normal guinea-pig serum when diluted 100 or 200 times with saline, develops the power to lower blood pressure and to increase capillary permeability as tested by the dye method. The permeability factor

(PF/Dil) originates also in the $\alpha_2$-globulin fraction of serum. It is easily distinguished from anaphylatoxin by the fact that its effect is not inhibited by antihistaminic agents and it shows no histamine-releasing action on the usual test preparations. PF/Dil is a protein and it is believed to be a proteolytic enzyme because its effect is abolished by soybean trypsin inhibitor. It is, however, different from all known proteases and, up to now, no appropriate *in vitro* substrate has been found for it. PF/Dil has been found in serum from other species[170] and lately its presence has been described in human plasma.[252] It has also been detected in intercellular fluid.[170]

Activation by dilution is explained as due to the diluting out of an inhibitor which normally forms a loose combination with the enzyme. It is, however, possible that the decisive factor in activation is the area of contact with glass. Recently, Margolis[161] has produced a permeability factor in guinea-pig plasma or serum by shaking it with very small glass beads (surface area about 200 $cm^2/g$). Up to the present this "contact factor" is indistinguishable from PF/Dil. It seems to be related also to the "pain-producing substance" of Keele and his co-workers.[3,160] Certain facts seem to point to the possibility that PF/Dil can be activated by other plasma constituents.[248]

The physiological significance of these various enzymes, enzyme activators and products of enzymatic reactions appearing in cell-free systems is very difficult to assess. Since allergic response can be elicited from isolated tissues and even single cells, humoral factors can hardly be considered essential for the *in vivo* reaction. There is no direct evidence showing that toxification of serum does occur *in vivo*. One indirect suggestion is that when animals are injected with an agent known to produce anaphylatoxin, the ability of their serum to form anaphylatoxin is decreased.[81] This can be interpreted as due to the exhaustion of the precursor by the previous injection. Another proof is that some of the agents which form anaphylatoxin *in vitro* also cause anaphylactoid phenomena when injected into whole animals. There are, however, some discrepancies: high molecular dextran which is the most active *in vitro* is ineffective in producing anaphylactoid phenomena and the smaller dextran molecules, the most toxic on injection, are inactive on anaphylatoxin formation.[87,214] Also agar and inulin, excellent anaphylatoxin-forming agents, have no effect on injection. The most curious contradition is that although rat serum yields the most potent anaphylatoxin, the rat is insensitive to it.[189,214]

It is impossible to decide on the basis of present evidence whether anaphylatoxin formation is an interesting artifact with no physiological significance whatever or one of the basic mechanisms of the allergic response. There is, however, one humoral factor which has been known to have an important bearing on at least certain types of allergic reactions. This humoral factor, complement, was implicated in the mechanism of the anaphylactic shock for the first time by Loeffler.[147] He showed that no anaphylactic shock could be elicited in complement-depleted animals. This requirement has been contested but the present-day tendency is to consider complement necessary for most types of allergic reactions.[17,23,28,192]

As mentioned above, in 1949 Ungar and Mist showed that protease activation in guinea-pig serum requires the presence of some factor destroyed by heating to 56° C.[273] These observations were later extended and the conditions of serum protease activation further speci-

fied.[271] It was found that no activation takes place in serum treated by ammonia or yeast which inactivate the fourth and third component of complement. Activation also failed to occur in sera in which complement was fixed by sensitized red cells. It was concluded from these studies that the presence of complement was probably necessary for the activation of serum protease by the antigen-antibody reaction. It was also suggested that complement or some component of it may play the role of activator or kinase for the proteolytic system of serum.

In 1953, Pillemer and his co-workers observed that activation of the plasma protease plasmin by streptokinase was followed by loss of complement activity.[202] As a result of further work, it was suggested that the first component of complement (C'1) may be a proenzyme which, when activated by plasmin, was capable of destroying C'2 and C'4.[140] Activation of C'1 requires the presence of calcium ions.[141,204] In 1954, the authors[144] suggested that complement fixation may be an enzymatic reaction "in which antigen-antibody would serve as a catalyst for the conversion of proenzyme to active enzyme."

In 1955, Becker[13,14,15] observed that the potent enzyme inhibitor di*iso*-propylfluorophosphate (DFP) inhibited complement in the presence of sensitized red cells. Further analysis showed that the antigen-antibody aggregate converts C'1 to an enzyme and this enzyme is sensitive to the inhibitory action of DFP. Since this inhibitor is fairly specific for esterases and proteases, the activated C'1 must be an enzyme of this nature.[142,143] Because of the comparatively high concentrations of DFP required for inhibition, it is more likely that the enzyme is a protease. However, no protein or peptide substrate has yet been found which could by hydrolyzed by activated C'1. Among the large number of synthetic peptides and amino acid esters tried by Ratnoff and Lepow[206] only some esters were attacked: the best substrate is N-acetyl-L-tyrosine ethyl ester, followed by tosyl-arginine methyl ester, benzoyl arginine methyl ester and three other less hydrolyzable amino acid esters. Activated C'1 is also partially inhibited by cysteine and some other sulfhydryl compounds. It is not inactivated by soybean trypsin inhibitor but can be inhibited by serum anti-protease. According to data available at present, this enzyme is distinct from all other known serum enzymes.

These investigations have failed as yet to specify the relation of the esterase derived from complement with the rest of the allergic response. There is particularly one point that has to be elucidated, that of the role of complement in the mechanism by which the antigen-antibody reaction evokes the cellular response. It is known that for some systems, such as immune hemolysis, complement is an essential requirement. It may also be so for rabbit platelets.[112] Guinea-pig lung, however, responds without complement, as shown by many observations. Rocha e Silva thinks that intercellular fluid may contain enough humoral factors to allow the reaction to take place.[224] Attempts at detecting complement in washed guinea-pig lung tissue gave entirely negative results.[268]

There is some evidence showing that some serum factor, even if not essential for the allergic response, may be able to increase it to a considerable extent. Guinea-pig lung perfused with homologous antigen releases histamine and shows signs of proteolysis. When, however, a small amount of fresh guinea-pig serum is added to the perfusion fluid, the allergic response, as evidenced by histamine release and proteolysis, increases ten or twenty fold.[268]

NATURE OF THE ENZYMES INVOLVED IN THE ALLERGIC REACTION

The investigations reviewed in the preceding sections leave the impression of a confused multiplicity of enzyme systems of doubtful identity and physiological significance. The fact is that none of the enzymes mentioned have been isolated in a state of satisfactory purity so that reactions attributed to a single enzyme may be due to mixtures of enzymes. It is also possible that several terms designate what may turn

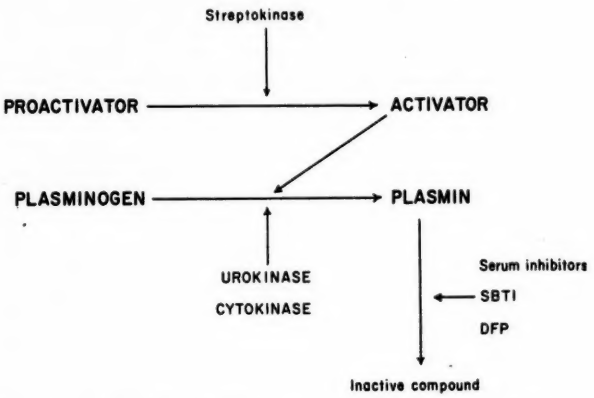


Fig. 1. *The Plasmin System.* The complete system including proactivator and activator, has been described in human blood only. Human activator, however, converts plasminogen of all species. SBTI = soybean trypsin inhibitor, DFP = di*iso*propylfluorophosphate.

out to be the same enzyme system. In order to clarify the situation somewhat, it may be appropriate to survey the various enzyme systems which have been implicated in the allergic response.

Only ten or fifteen years ago, the enzymatic theory of allergy could be expressed in much simpler terms than today. In 1944, Bronfenbrenner[26] showed in this Journal a simple diagram representing the activation of "plasma trypsin" by dissociation of its complex with the antitrypsin of serum. A few years later when serum fibrinolysin became better known, it was convenient to think in terms of this system. Ungar and his coworkers, although suspecting that fibrinolysin may not be a well defined enzymological entity, spoke of profibrinolysin activation and called the resulting enzyme fibrinolysin, simply because it was detected by its lytic action on fibrinogen or fibrin.[260,262,271,273] Today, fibrinolysin or plasmin is the best known of all the circulating proteases. It has been characterized by its optimum pH, its substrate specificity (particularly on synthetic amino acid esters) and its inhibitors.[58,30,31,131a,257a] It is distinct from all the digestive proteases as well as from proteolytic enzymes found in tissues.[223]

Its most distinctive property is the fact that it results from the conversion of its inactive precursor, plasminogen by a specific activator.[181] This activator, a protease itself, as shown by its ability to hydrolyze the synthetic substrate lysine ethyl ester,[257] exists in normal serum as an inactive precursor, called proactivator. The proactivator-activator system

has only been found in human blood but human activator can act on plasminogen from any species. The only substance which is known with certainty to convert proactivator to activator is the bacterial product, streptokinase. The latter is probably not an enzyme and its effect on the proactivator seems to be the result of a stoichiometric combination.[181]

Streptokinase has a weak and variable effect on plasminogen from species other than man. Most of the reports of activation are probably due to the fact that the test system was contaminated with human proactivator. It is well known that even the purest fibrinogen preparations contain some plasminogen and proactivator as impurities.[257] Many contradictory results published in the literature are due to this fact.

The diagram shown in Figure 1 summarizes our present knowledge of the plasmin system. It shows that besides its specific activator, plasminogen can be activated by kinases isolated from tissues[6,7,8,53] and from urine.[9,297] The urinary activator, urokinase, has been the object of several studies.[79,123,131,203] It was prepared in a fairly high state of purity and was found to be similar to the serum activator in its ability to hydrolyze lysine ethyl ester. It was seen above that urokinase increases in the urine of guinea pigs submitted to anaphylactic shock. Urokinase has been shown to exist in the urine of all species and it seems to act on plasminogen of all sources with, however, some quantitative differences.[172] It is not known whether urokinase represents the form of elimination of the serum activator. This seems at present unlikely since the serum of most animals lacks plasminogen activator.

It is more likely that urokinase originates in the tissues. The presence of a plasminogen activator or cytokinase in various tissues was described by Permin,[200] and confirmed by other workers. The kinase present in endometrial extracts may be responsible for the fluidity of menstrual blood. It behaves like a protease itself but has a different substrate specificity from plasmin. It may have some nuclease activity also.[201] It is likely that in many cases where fibrinolysin was observed *in vivo* but could not be produced *in vitro*, activation was due to these tissue kinases.

There is no direct evidence that protease activation recorded in allergic conditions did in fact involve the plasmin system. The relation of the "serofibrinokinase" described by Ungar[271,273] to plasminogen activator remains uncertain, until more studies are done using the synthetic substrates specific for the activator and for plasmin.

There is some doubt about the individuality of plasmin as a single enzyme. Recently, it has been compared with chymotrypsin which is known to exist under a number of slightly different forms according to the mode, the degree and other conditions of activation of different chymotrypsinogens.[184] There is also some doubt about the identity of plasmin preparations from different species.

There is good reason to believe that plasmin is not the only circulating proteinase. Comparison of the results obtained by different methods suggests that activation of serum by various types of kinases from tissues, serum, urine and microorganisms does not yield the same enzyme.[235,236] The principal methods used for the study of serum proteases can be summarized as follows: (a) fibrinolytic and fibrinogenolytic techniques (clot lysis,[145a] fibrin plate, [181] fibrinogenolysis followed by clotting of the remaining fibrinogen),[56,205,269,273] (b) hydrolysis of other protein substrates: [66,112,223] casein, gelatin, hemoglobin, endogenous tissue proteins, et cetera; (c) hydrolysis of synthetic peptides or amino acid esters.[236,257a]

Even such technical detail as the protein precipitant may be of decisive importance: clotting fibrinogen by thrombin, instead of precipitating it with trichloracetic acid increases the sensitivity of the method by a factor of 1000.[119] This represents not merely a quantitative difference but suggests that different enzyme actions may be measured.

Besides proteinases, blood and tissues are known to contain a number of peptidases[37,60,61,239,300,302] (dipeptidase, tripeptidase, leucine aminopeptidase, et cetera) which have not yet been related to allergic phenomena. This omission is the more regrettable since some of the highly specific proteases mentioned above may in fact be peptidases. One of them, plasminogen activator, probably acts by splitting off a small peptide fragment from plasminogen, as suggested by the mechanism of activation of trypsinogen and chymotrypsinogen. Both serum activator and urokinase are able to hydrolyze lysine ethyl ester.[131,257]

The esterase produced by activation of C'1 by the antigen-antibody complex may also be one of these specific proteases. Ratnoff and Lepow[206] were unable to detect any unequivocal effect on a number of protein substrates but the enzyme, as seen above, hydrolyzes some amino acid esters. C'1-esterase follows the pattern of being derived from an inactive precursor. The mechanism of this activation, which requires the presence of calcium ions, may be similar to that of trypsinogen. Let us note here that C'1-esterase is not affected by soybean trypsin inhibitor but is inactivated by serum inhibitor and high concentrations of DFP.[14,15]

If anaphylatoxin is an enzyme, which is far from being proved, it may belong to the category of specific proteases since it does not attack ordinary protein substrates. There is somewhat better evidence for the enzymatic nature of Miles' permeability factor (PF/Dil).[295,296] It differs from C'1-esterase by the fact that it is inactivated by soybean trypsin inhibitor. However, it does not seem to digest the usual protein substrates and there is no mention in the literature of its effect on synthetic substrates.

PF/Dil may be closely related to kallikrein which is the best known of all specific proteases and can be considered as their prototype. Its link with allergy is based only on Beraldo's observations[21] but it is probable that further investigation will reveal more about the role of the kallikrein-kallidin system in the allergic response. The only known substrate of kallikrein[63] is kallidinogen, a protein belonging to the $\alpha_2$-globulin fraction of serum. Kallikrein is, therefore, similar to the enzyme renin which acts only on hypertensinogen (also in the $\alpha_2$-globulin fraction) to form hypertensin. It is to be noted that renin can also form kallidin. Kallikrein is present in circulating blood as the inactive precursor kallikreinogen which can be reversibly activated by dilution, pH changes, heating, increased contact with glass and also by the action of proteinases such as trypsin and papain. Other procedures (acetone precipitation, salting out) result in the irreversible activation of a slightly different enzyme, called kallikrein II.

Figure 2 summarizes present-day knowledge of the kallikrein-kallidin system. It should be added that the presence of kallikrein has been described in a number of tissues and in urine. It is difficult to say whether kallikrein prepared from these sources is identical with the circulating enzyme. It is intriguing that a potent and highly purified urokinase had all the properties of kallikrein: it lowered blood pressure in the dog at the dose of 0.5 $\mu$g/kg and catalyzed the formation of a kallidin-like substance from dog serum globulin (unpublished observations by Ungar and Sezesny).

Since no pure preparation of kallikrein is available and no reliable enzymological studies are found in the literature, the only criterion for the activity of this enzyme is the formation of kallidin or bradykinin. Kallidin formation has been attributed to other proteases, such as trypsin, plasmin, renin, et cetera, but Werle believes that it is due to contamination by traces of kallikrein.[292]

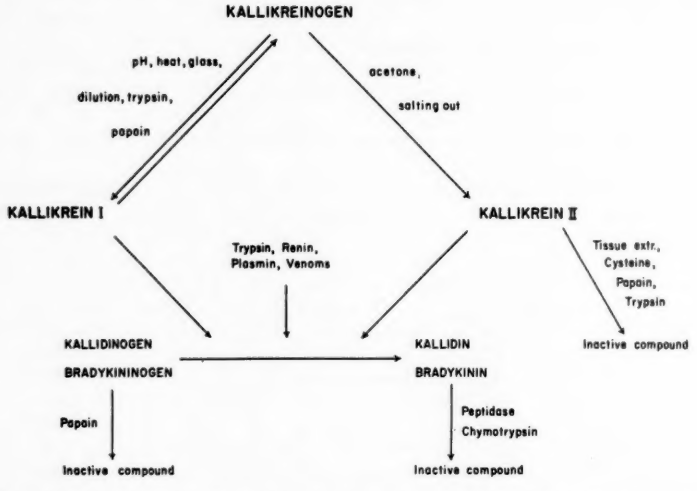


Fig. 2. *The Kallikrein-Kallidin System.* Kallikrein is a typical specific protease which is not known to act on any other substrate than kallidinogen. Bradykinin (probably identical with kallidin), which is known to appear in anaphylactic and peptone shock, can also result from other enzymatic actions on the precursor.

Protease activation in cells is even more difficult to relate to known cellular enzymes. It has been known for a long time that all cells contain proteases called cathepsins, active at acid pH. It was believed that cathepsins were primarily autolytic enzymes which became active when, after the death of the cell, the pH fell to their range of effectiveness. More recently, however, an increasing number of tissue proteases have been found active at physiological pH values. These enzymes, often called cathepsin C, may be involved in the observations of Hayashi,[91,92] Herberts[102,103] and Mongar and Schild,[175] because of the role of SH inhibitors.

There is no doubt that leukocytic enzymes play an important role in various allergic reactions. It is therefore regrettable that we know so little about them. The considerable amount of older literature is practically useless today because of the rapid obsolescence of enzymological techniques.[12] Leukoproteases, as described by Opie[191] do not seem, in any way, different from cathepsins found in other types of cells. There are no reliable studies indicating different enzymes being present in different classes of leukocytes. The presence of a chymotrypsin-like enzyme in mast cells[20] still awaits confirmation.

The skin has been the object of many studies and several proteases[19,163,-164,267,289] were isolated from it. The acantholytic enzyme described by Stoughton and Novak[253] is the one that offers most resemblance to the protease described in inflamed rabbit skin by Hayashi.[91,92]

Lung tissue plays an important role in experimental allergy and a better knowledge of lung proteases would certainly help the understanding of many obscure phenomena. Dannenberg and Smith[40,41] have found in beef lung, in addition to the usual peptidases, two proteinases with maximum activities at pH 4 and 8, respectively. Proteinase II, active at high pH, is partially inhibited by substances which block SH groups. It is, however, probably not a pure enzyme but a mixture of several proteases one of which is SH dependent.

The only tissue proteases which are known to be formed by activation of precursors are the digestive enzymes of the pancreas. A great deal is known about the mechanism of this activation[184] and may supply an analogy for other similar processes. During activation, trypsinogen loses a hexapeptide (called activation peptide) and the rest of the molecule undergoes a rearrangement which creates the active center of the enzyme. Chymotrypsinogen activation is somewhat more complex and different conditions of activation result in slightly different chymotrypsins. However, here also the main change is release of a peptide with rearrangement of the protein molecule.

No activatable protease precursors have been isolated from other tissues. It is, of course, possible that the precursor is so unstable that it is activated during the extraction procedure. It should be mentioned that there has not been any systematic effort in this direction. There have been suggestions that protease activation in cells may be determined by metabolic changes. Increased lactic acid production by anaerobic glycolysis may lower the pH to the range of activity of cathepsins.[222,251] Early occurrence of protease activation is contrary to this assumption.[299]

There is, however, one activation mechanism which is theoretically more likely: the increased availability of reactive SH groups. Most native proteins have few freely reacting SH groups, they are either involved in S-S bridges or are masked by surrounding hydrogen bonds or Van der Waals forces. On denaturation, these SH groups are "unmasked" and, on becoming reactive, could activate the cathepsins. This possibility will be discussed in the next section in connection with cellular excitation and the allergic response.

Activation of plasma proteases by tissue factors was discussed previously. The reverse mechanism, that is the way in which plasma proteases or exogenous enzymes, like trypsin or papain, act on the cell, is still unknown. According to current views, these enzymes could not enter the cell. If they act on the surface of the cell, they may activate there some intracellular protease which, in turn releases histamine and produces the other changes. It should be added that very little is actually known about what can or cannot enter the cell.

One last factor that further complicates the situation is the simultaneous presence of various protease inhibitors in tissues and body fluids. Serum "antitrypsin" which has been known to exist since the end of the last century,[106] appears today as consisting of at least three different substances, at least in human blood.[207,244-246] This does not include the inhibitor of kallikrein which is supposed to form a reversible combination with the enzyme. It is also possible that the inhibitor of Miles' factor PF/Dil which seems to be an $\alpha_1$-globulin is also a different substance.[295]

Other inhibitors have been described in tissues. Hayashi found an inhibitor in the globulin fraction of rabbit skin and also in monocyte cultures.[91,92] Another inhibitor was prepared from the same sources, but it was extractable with ether and alcohol. It is not known whether any

of these substances are identical with other skin protease inactivators,[163,164] one of which is specific for skin protease.[18]

Generally speaking, enzyme inhibitors may operate in two different ways. They can form a complex by stoichiometric combination with the enzyme. The best known example of this type of inactivator is the pancreatic trypsin inhibitor.[136] The enzyme-inhibitor complex may represent a reversible or an irreversible combination.

In other cases, the inhibitor is an enzyme itself and inactivates the protease by hydrolyzing it. Ungar and Adler[265] have described a peptidase in guinea-pig serum which they believe to be one of the protease inhibitors. The full cycle of the plasmin system may therefore be described as follows: plasminogen converted into plasmin by plasminogenase (activator) and plasmin changed to an inactive compound by plasminase (inhibitor).[181,275]

It is not known whether all the enzyme systems just surveyed play a role in the allergic response. It is even possible that the principal factor is some as yet unidentified or even undetected enzyme. In the next section an attempt will be made to trace the sequence of enzymatic events which may lead to the allergic response.

## ENZYMATIC EVENTS AND CONTROL OF ALLERGY

It is obvious from the preceding survey that the facts concerning the enzymatic mechanism of allergy do not fall automatically in place. In fact, in the present state of our knowledge, it appears impossible to formulate a coherent hypothesis without having recourse to some speculation. In this section, we shall try to make such an hypothesis or rather two of them because the cellular and humoral events will have to be considered separately. In the accompanying diagrams the solid lines indicate what the reviewers consider as established facts while the dotted lines represent hypothetical possibilities.

The primary site of most allergic reactions is the antibody containing cell. Even the older literature mentions observations which suggest that the cellular antigen-antibody reaction requires an active participation of the host cell. Richet[208a] showed that general anesthesia prevents or at least reduces the severity of anaphylactic shock. The fact, mentioned above, that the sensitized cell does not respond to the antigenic stimulus unless its morphological integrity and its metabolic processes are intact, suggests that the reaction has an excitability component. The antigen-antibody reaction does take place in the absence of oxygen or in the presence of metabolic inhibitors but it fails to bring about stimulation of the cell.[175,194] Agents which are able to bypass the stage of cellular excitation, such as some synthetic histamine liberators, do not have the same requirements. Their effect is even increased by lack of oxygen and the presence of cyanide.[175]

It appears therefore that the allergic response may be the result of cellular excitation in the course of which the mediators (histamine, 5-hydroxytryptamine, etc.) are released by a mechanism similar to that of potassium loss. This mechanism is commonly believed to be a sudden increase in membrane permeability. There has, however, been a tendency in recent years to revise the classic permeability concept. Evidence has been produced which shows that excitation is accompanied by a structural rearrangement of certain cell proteins, similar to what occurs in reversible denaturation.[266] Such a rearrangement, besides being able to convert inactive precursors into active enzymes, also changes the distribution of electrical

charges in the cytoplasm and may set free inorganic and organic ions. Further discussion of this problem is to be found in a recent review.[264]

The insulin requirement observed in histamine liberation by dextran,[72] further supports the existence of an excitability component in the allergic reaction. It has been shown that insulin is capable of maintaining in muscle

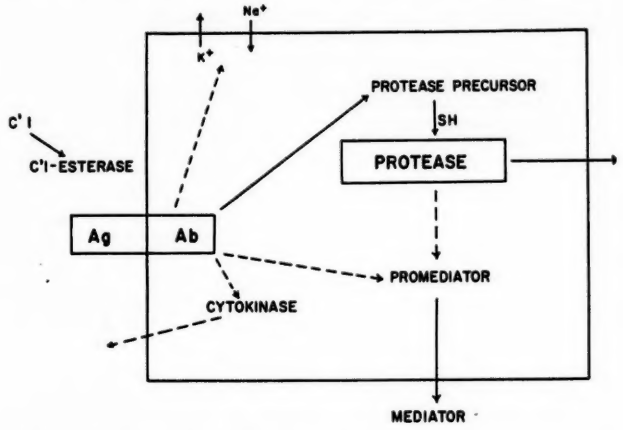


Fig. 3. *Possible Mechanisms of Protease Activation in the Cell.* Established pathways are indicated by solid arrows, unconfirmed or hypothetical mechanisms by broken arrows. The probability of cellular excitation being caused by the antigen-antibody reaction is indicated by the exchange of the K+ and Na+ ions.

cells a high degree of electrical polarization by increasing potassium concentration and decreasing sodium content of the cell.[36,301] The necessity of this hyperpolarization for the efficacy of the allergic stimulus is a problem to be elucidated. It is interesting to note that histamine release by substance 48-80 is not influenced by insulin.[72] This can be correlated with the observation that dextran releases potassium from the cell[86] and 48-80 does not.[198,199]

There is an increase in reactive SH groups during cellular excitation.[276] This may, in view of the SH dependence of cellular proteases, represent a factor of activation. These enzymes may be in a relatively inactive state in the cell because of the scarcity of free SH groups and be suddenly activated when the SH groups of proteins are unmasked by the denaturation-like changes. The latter could activate the enzymes more directly by freeing their own reactive SH groups which are probably part of the enzymatic site.

The diagram shown in Figure 3 represents the various ways in which the allergic response may be elicited in the cell. Union of the antigen with the intracellular antibody creates the stimulus with the possible help of the complement-derived enzyme. This sets in motion either the permeability changes postulated by the membrane theory or the redistribution of electrical charges which follow the structural rearrangement of protein molecules. According to available experimental evidence, surveyed above, an active protease appears in the cell and diffuses out. Whether this protease is directly responsible for the release of mediators or proteolysis

and mediator liberation are parallel phenomena due to a common cause, is at present uncertain.

The diagram also attempts to show the immediate relation of the cell with its humoral environment. It was seen above that some tissues, especially those of the guinea pig are able to react to the antigen in the

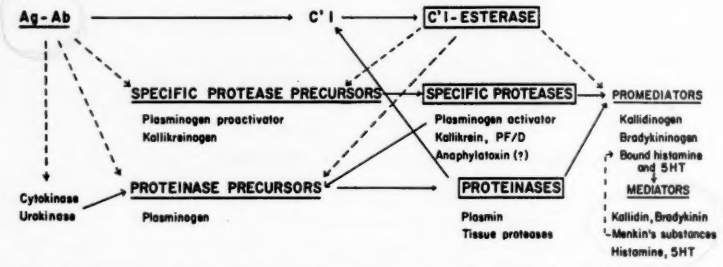


Fig. 4. *Possible Mechanisms of Protease Activation in Body Fluids.* Established pathways are indicated by solid arrows, unconfirmed or hypothetical mechanisms by broken arrows. For detailed discussion of the various mechanisms represented, see text.

complete absence of any humoral factors. Other preparations (isolated dog and rabbit tissues) are only responsive in the presence of whole blood or serum. Even guinea-pig lung or intestine reacts better when fresh serum is added to the preparation.[133,268] It is therefore probable that some fixed cells behave in a manner similar to that of red cells in a hemolytic system: the sensitized cell converts C'1 to an esterase which, in some yet unknown way, contributes to the reaction.[16]

On the other hand, the protease formed by this stimulus as well as the cytokinases produced by the reacting cell diffuse out and are probably responsible for the fibrinolysis observed in whole animals submitted to allergic stimuli.

The physiological significance of humoral reactions, such as anaphylatoxin formation, serum protease activation and bradykinin or kallidin formation, is still uncertain. It is most likely that, according to the type of allergic reaction, the basic enzymatic mechanisms are combined in a different manner. Figure 4 attempts to summarize these basic mechanisms and their possible combinations. Some of these combinations have been proved to occur, others are hypothetical. The figure represents a modified form of diagrams published previously[260-263] and adopted by a number of authors.[35,113,124,232]

The main function of the enzymatic reactions seems to establish a link between the allergic stimulus (antigen-antibody reaction or its equivalent) and the release of mediators. As can be seen from the diagram, this objective can be reached by steps of varying complexity. The typical reaction probably involves activation of a specific enzyme (C'1-esterase, plasmin activator, or kallikrein) which in turn activates a proteinase. The proteinase then acts on the promediator and releases the mediator. It is probable that this chain of reactions can be shortened so that the specific protease or peptidase acts directly on the promediator. It is also possible that, in certain cases, an even more complex interaction of enzymatic processes occurs.

There can be little doubt that such mediators as kallidin, bradykinin and

Menkin's substances[167] are released by enzymatic action. The problem is different for histamine or 5-hydroxytryptamine which are not known to form hydrolyzable linkages with proteins. The problem was discussed at a Ciba Symposium in 1955[153,198,214,263] and more recently by Paton.[199] At best, one can say that there is a correlation between histamine release and proteolysis but there is no definite evidence of a causal link. It should be pointed out it is not essential for histamine to be attached to proteins by a peptide linkage to be released by protease action. This can occur also if it is held by an ionic or hydrogen bond. Even a slight denaturation-like change, such as has been observed in cellular excitation, is sufficient to liberate the organic cation. Such a change may also occur as a result of incipient proteolysis. It is currently assumed that the first step of the action of proteases is denaturation of the substrate.[146,183a]

Jensen[115] believes that protease activation may result in direct action of the enzymes on structural proteins, without necessarily going through the release of mediators. The activated proteases may damage directly the capillary endothelium and bring about the characteristic increase in vascular permeability.[197] The later morphological changes observed by Hayashi may also be interpreted as being due to the action of the protease activated during the first few minutes of the allergic response.

Other interesting possibilities are the dissociation of lipoprotein and mucoprotein complexes under the influence of the protease. Paradoxically, however, the lipid separated has an inhibitory effect on protease.[210] The release of mucopolysaccharides, such as heparin, in anaphylaxis is of course well known. Besides, Hayashi[65,98,99] observed that normal connective tissue shows little metachromasia but the metachromatic reaction is intense at the very early stage of the Arthus reaction. Metachromasia can also be induced by intracutaneous injection of the protease extracted from inflamed tissue, or by application of the enzyme to tissue sections. This is interpreted as being caused by the release of the polysaccharide moiety from the mucoprotein molecule. Since high molecular carbohydrates are anaphylactoid agents capable of forming anaphylatoxins and initiating histamine liberation, their release may be an important mechanism by which proteases act in the allergic reaction.

A frequent objection to the enzymatic theory of allergy is that protease activation is not specific for the allergic response[28,127,128,182,282] since it is observed in all types of tissue aggression, such as trauma,[24,149,150,284] thermal and radiation injury,[33,138,267] direct action of bacterial toxins,[294] and animal venoms.[210a,213] This, of course, is true and protease activation may be a fundamental cellular and humoral response to all types of stimuli which disturb the homeostatic balance.[115,260,262] It should be pointed out that, in its final mechanism, the allergic reaction is not different from the other cellular and humoral responses to injury. The only difference lies in the state of sensitivity of the individual to the particular stimulus.

It is, however, possible that there are differences between the way cells react to antigenic stimuli and to some more directly physical or chemical aggressions. One such difference may be the requirement of intact cell structure and excitability. Perhaps also some intensive stimuli, such as heat, may involve enzymatic mechanisms not activated by allergy or inactivate others which are implicated by milder stimuli.[256]

It is obvious that, if enzymatic processes play an important role in the mechanism of allergy, we should be able to block the allergic response

by the use of enzyme inhibitors. Many of the enzyme inhibitors which have been used in experimental work are highly toxic because they have an affinity for widespread and sometimes vitally essential enzymes. Such is the case, for example, of DFP which was synthesized as a "nerve gas" because of its potent inhibitory effect on cholinesterase.

The only non-specific enzyme inhibitors mentioned in the literature for their possible anti-allergic effect are the citrates and certain thiol compounds. Use of citrates was proposed by Rocha e Silva[211] because of their inhibitory action on anaphylatoxin formation and on histamine release from rabbit blood.[112] Topical application of an isotonic (3.8 per cent) solution of trisodium citrate has been reported to have a beneficial effect in allergic dermatitis.

The thiol compounds have been recommended by Herberts for their blocking action on the cellular proteases activated in the antigen-antibody reaction.[102] A number of synthetic thiols and thioethers investigated were found not only to inhibit the lung protease but also to prevent anaphylactic shock in the guinea pig. The most suitable for clinical use appeared to be *p*-methylbenzolmethylthioether.[104] There is no record of clinical trials.

Among the more specific protease inhibitors, the only one suitable for clinical use is the soy bean trypsin inhibitor. This is a pure protein,[134,135] available commercially in crystalline form. Its use was recommended by Rush and Cliffton[226] but, at present, the material is too costly for extensive use. Although the protease inactivator of serum may play an important role in the physiological control of various proteolytic processes, it is not yet available in a form suitable for therapeutic use.

There is some evidence showing that certain drugs with known anti-allergic activity are also protease inhibitors. Salicylates, pyrazolone derivatives (aminopyrine, butazolidine) and other antipyretic drugs were shown to counteract certain experimental allergic reactions.[175,247] These same drugs were shown to inhibit plasma proteases (presumably plasmin) *in vitro* at concentrations which can be realized in the circulating blood of subjects treated with therapeutic doses.[270] It is therefore possible that, whatever anti-allergic effect these drugs possess, is due to an enzymatic block at some point of the diagram shown in Figure 4.

More interesting is the case of the antiphlogistic hormones of the adrenal cortex and pituitary which are among the most potent anti-allergic drugs. A number of mechanisms have been suggested for these drugs, such as the inhibition of antibody formation[67] and the prevention of histamine synthesis in the tissues.[231] All these mechanisms may contribute to their anti-allergic effect but neither can explain the rapid action of the hormones in certain experimental and clinical allergic reactions. Administration of ACTH or cortisone can suppress allergic symptoms within a few hours.[183,272] Addition of small amounts of cortisone *in vitro* to a monocyte culture is able to prevent cell damage produced by the homologous antigen.[97]

Recently, evidence was produced for the inhibition of anaphylatoxin formation in sera to which hydrocortisone had been added *in vitro*.[105] Ungar, Damgaard and Hummel[269] in 1951 were unable to obtain any effect *in vitro* on protease activation. They observed, however, an increased antiprotease activity in the serum of animals treated with ACTH or cortisone. The opposite effect was observed with sera from animals treated with desoxycorticosterone or growth hormone. These observations have been confirmed by many workers.[52,76,137a,165,173,250] Quite recently, the same effect was shown for the synthetic compounds, prednisone, predni-

solone, 9-α-fluorocortisol,[116] medrol and aristocort.[229] In all these studies, there was a good correlation between clinical activity of the compound and its effect on protease inhibitor content of serum. It is possible that the particular protease inhibitor which is increased by the action of the hormones is an enzyme itself.[265] In the complex maze of enzymatic effects, shown in Figure 4, one can say that there is hardly anything that an enzyme does which cannot be undone by another enzyme.

An interesting problem is that steroid hormones are ineffective in the acute anaphylactic shock of the guinea pig while[43,139,159] they are able to inhibit shock in mice and rats[62,29,183] and have a definite effect on local allergic reactions in many species.[110,272] This may point to some enzymatic differences.

Species differences have to be kept in mind every time some experimental allergic condition is influenced by a potential therapeutic agent. In the particular field just surveyed, there are extremely few investigations conducted in human subjects. The clinical investigator would find the field a fruitful one, with techniques already worked out and full of interesting practical possibilities.

## CONCLUDING REMARKS

Proteolytic phenomena have been observed in many types of allergic reactions in anaphylactic or anaphylactoid shock of the whole animal, in isolated tissues and cells and in cell-free body fluids. In most instances, protease activation seems to result from the interplay of many factors, some cellular, some humoral.

After having surveyed these factors, one cannot help regretting the appealing simplicity of the early enzymatic hypothesis. The present untidy situation, as it is summarized in Figures 3 and 4, is far removed from the unitary concept which was the aim of the original enzyme theory.

There are, however, hopeful signs of some unifying ideas emerging from the tangle of data. There appears to be, among the $\alpha_2$-globulins, a common protein matrix, particularly involved in the allergic response and related reactions. The interesting effect of polysaccharides on the activation of enzyme systems points to the possibility that splitting of mucoproteins plays some particular role at one specific point. A further interesting fact is that wherever a protease is discovered, it is always closely followed by a more or less specific inhibitor. All this points to the probability that we are dealing with some activator-enzyme-inhibitor complexes, deriving from each other and interacting in a presumably ordered and delicately balanced sequence.

Similar problems have arisen in other fields, for example in intermediary metabolism, and are being successfully elucidated. The problem of allergy, however, is at a far less advanced stage and important facts still remain to be discovered to link together the loose bits of information. There are also conceptual obstacles to integration of knowledge in a field where problems of cellular morphology and excitability, immune reactions and pharmacological activity mingle with those of enzymology and protein chemistry.

Future progress will greatly depend on our fast growing knowledge of protein structure and its biological significance. By a small change in molecular configuration an inert precursor can be converted to a potent enzyme which in turn is inactivated by a further modification of its structure.

An antibody-containing cell is excitable by the homologous antigen which is otherwise ineffective. This stimulation brings about structural rearrangements in certain cell proteins and may, in this fashion, initiate the whole cycle of enzyme activations and inhibitions with subsequent release of mediators and production of local and systemic reactions.

Similar phenomena occur after extracellular antigen-antibody reaction. Discussion of this would only lead to a pointless reopening of the old cellular *vs.* humoral controversy. It is probable that the responsive site of the allergic reaction is always cellular but the receptive site may be both cellular or humoral. Purely cellular or purely humoral allergic responses are merely interesting and instructive experimental artifacts.

Enzymatic phenomena represent only one aspect of the allergic problem. Whether they occupy the central position that is sometimes assigned to them, or their significance is merely incidental, remains to be elucidated.

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**THE BRIGHTEST LIGHT**

"Imagine activities in the brain shown by little points of light. Of these some stationary, flash rhymically, faster or slower. Others are travelling points, streaming in serial trains at various speeds. Suppose we choose the hour of deep sleep. Then only in some sparse and out of the way places are nodes flashing and trains of light-points running. The great knotted head-piece of the whole sleeping system lies for the most part dark.

Should we continue to watch the scheme we should observe after a time an impressive change which suddenly accrues. In the great head-piece spring up myriads of twinkling stationary light, and myriads of trains of moving lights of many different directions. The great topmost sheet becomes now a sparkling field of rhythmic flashing points with trains of traveling sparks hurrying hither and thither. The brain is waking and with it the mind is returning. It is as if the Milky Way entered upon some cosmic dance. Swiftly the head-mass becomes an enchanted loom where millions of flashing shuttles weave dissolving patterns. The body is up and rises to meet its waking day."—Sir Charles Sherrington, *Man on His Nature*, 1st edition, Cambridge University Press, 1941, p. 223.

# Editorial

*The opinions expressed by the writers of editorials in the* ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

## IMMUNOLOGICAL UNRESPONSIVENESS

Lack of response to antigenic stimulation has been the subject of considerable investigative work during recent years. Data of profound interest for our understanding of immunological processes have been obtained by the detailed study of four mechanisms of immunological unresponsiveness:

1. Agammaglobulinemia—the congenital or temporary lack of production of antibody protein.

2. Destruction of the antibody producing cells by external influences, such as irradiation.

3. "Immunological paralysis"—the inhibition of the production of one particular antibody by the introduction of large amounts of the corresponding antigen. And

4. "Acquired tolerance," which can be "defined as an induced state of specific non-reactivity toward a substance that is normally antigenic—a non-reactivity, moreover, that is due to a primary failure of the machinery of immunological response" (Billingham, Brent, and Medawar in "The relation of immunology to tissue transplantation." Ann. New York Acad. Sc. 59 (3), p. 409, 1955). This concept evolved from the following basic observations: The introduction of homologous cells by graft or other methods is accepted as long as the immunological mechanisms are undeveloped, that is during fetal life or (sometimes) right after birth, whereas the mature animal destroys such grafts by antibody production. Animals injected during fetal life (or, at any rate, before immunological maturation) with homologous cells will accept during later life grafts from the same donor. They have somehow lost the ability to "recognize" these cells as foreign.

During recent days, four papers have come to the attention of this writer, which show how the studies of these phenomena complement each other and provide deeper insight into the physiology of antibody production:

The immune reaction which causes the rejection of homologous cells varies greatly in intensity. Cells from lymph nodes or peritoneal exudate must find a considerable degree of acceptance as witnessed by their continued production of antibody after introduction into the host. Harris *et al* just reported, that prompt rejection can be provoked by injecting leukocytes and other homologous cells previous to the introduction of the antibody producing lymph node cells. (Jour. Exp. Med., 108, 21, 1958)

On the other hand, destruction of the antibody producing apparatus by irradiation provides a host which may accept not only homologous cells but also those from a different species. Thus immune reactivity can be restored to the irradiated host by "recolonization" with antibody producing cells (such as bone marrow suspensions) from a foreign species (see C. C. Congdon, Blood 12, 746, 1957).

LaVia *et al* (Proc. Soc. Exp. Biol. & Med., 98:215, 1958) recently demonstrated this in an ingenious manner: Normal rats are able to produce antibodies against bacteria, but not against certain solute proteins such as bovine serum protein; rabbits produce antibodies against either type of antigen. If irradiated rats are "recolonized" with cells from rat embryos, they respond to injections with typhoid vaccine plus albumin in the "rat manner," that is by antibody production against the former, but not against the latter antigen. Irradiated rats "recolonized" with rabbit cells also recover their ability to produce antibodies. However they respond to the injection of the mixture of the two antigens like a rabbit, in that they produce antibodies to either antigen.

"Acquired tolerance" to tuberculin is reported by Weiss (J. Exper. Med., 108:83, 1958) for guinea pigs injected with tuberculin during fetal life. This finding supplements similar data previously collected with antigens like serum albumin and bacterial vaccines. Thus it appears that "acquired tolerance" is not restricted to homologous cell antigens, but applies to immunological response in general.

However, "acquired tolerance" is restricted by several factors. Thus the newborn rabbit is not able to acquire tolerance to tuberculin, though it does show this phenomenon with antigens like heterologous serum proteins (Smith and Bridges, Jour. Exp. Med., 108:227, 1958). This paper also points up an important quantitative aspect of "aquired tolerance" by providing data according to which the production of this phenomenon in the newborn rabbit depends on the injection of relatively large amounts of antigen (in the order of 10 mg. or more), whereas smaller doses are without effect. This establishes a link to the phenomenon of immunological paralysis of adult life. In this connection it should be remembered that both "acquired tolerance" and imunological paralysis are strictly antigen specific.

A. J. W.

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**PREVENTIVE MEDICINE**

"The understanding of the problems of mental health differs in some remarkable respects from the understanding of the problems of physical health. Although psychiatry is one of the oldest branches of medicine, scientific psychiatry is still relatively in its infancy as compared to internal medicine. As far as prevention goes, it is in the neonatal stage. The total prevention of personality disorders cannot be planned for with any self-assurance; however, as far as the understanding of health promotion and the nature of mental health is concerned, there are many more people acquainted with the nature of mental life than there are people acquainted with the nature of physical life. Relatively few people are aware of the appearance of living organs. Few have seen hearts, lungs, stomachs, intestines, kidneys, brains, etc., in the living state. However, practically everyone is familiar in some way with personalities and the problems of personalities."—Hugh Rodman Leavell, M.D., Dr. P. H. and E. Gurney Clark, M.D., D. P. H., *Preventive Medicine for the Doctor in his Community*, McGraw-Hill Book Company, Inc., 1958.

# Papers of Interest

Earle, B. V.: Fatal agranulocytosis due to promazine hydrochloride. Lancet, 2:925 (Nov. 9) 1957.

Strom, J.: Probenecid-Penicillin allergy: Allergic mucocutaneous reactions following treatment of Haemolytic streptococci infections with penicillin preparations containing probenecid. Acta paediat., 46:387-395 (July) 1957. (In English)

The total incidence of side-effects in the patients treated with probencid-penicillin preparations was 30.5 per cent—fifty-eight of 190 patients). Urticaria occurred in six and a maculopapular rash in fifty-two. Bullous and pseudomembranous type of reaction affecting skin, mucous membranes and the conjunctiva occurred in a seven-year-old girl treated with Vebecillin.

Nolen, W. A., and Dille, D. E.: Use and abuse of antibiotics. New England J. Med., 257:33 (July 4) 1957.

Antibiotic agents were administered for 2,936 separate illnesses. On 1,395 occasions administration was warranted, but on 1,541 occasions, it was not indicated.

McBay, A. J., and Katsas, G. G.: Glutethimide (Doriden®) poisoning. New England J. Med., 257:97, 1957.

Study of five cases, four, fatal.

Brunson, J. G.: Increasing prevalence of unexplained liver necrosis. New England J. Med., 257:52, 1957.

Review of the autopsy and clinical records of 3,229 University of Minnesota patients during the period 1955-1956. In seventy-two per cent of the fifty-one patients when seen correlation was noted between hepatic necrosis and the administration of sympathomimetic amines.

Rapaport, Howard G.: Psychosomatic aspects of allergy in childhood. J.A.M.A., 165:812 (Oct.) 1957.

Combined attention to the whole individual—body and mind—produces better therapeutic results than attention solely to either one or the other.

Allanby, K. D.: Deaths associated with steroid hormone therapy: an analysis of 18 cases. Lancet, 1:1104-1110, 1957 (Med. Lit. Abstracts J.A.M.A., 165:412 (Sept.) 1957.

In nine of the deaths steroid hormones "could be fairly blamed" and the drugs were probably responsible for two more. In three others death was "quite possibly hastened or contributed to by cortisone or corticotropin." Signs and symptoms of infection were suppressed.

Leslie, Alan, and Simmons, Daniel H.: Evaluation of the bronchodilator, Caytine (JB-251), Am. J. Med. Sci., 234:321, 1957.

The drug was evaluated in thirty-two male patients suffering from chronic emphysema-fibrosis-bronchiectasis associated with bronchospasm. In the thirty-two patients there was a significant increase in mean inspiratory and expiratory vital capacities.

Galdston, Morton; and Geller, Jack: The effects of aminophylline and Diamox alone and together on respiration and acid-base balance and on respiratory response to carbon-dioxide in pulmonary emphysema. Am. J. Med., 23:183-196, 1957.

When aminophylline (0.5 mg), is injected intravenously and acetazolamide (2.9-7.2 mg/kg body weight) is given orally to patients with advanced pulmonary emphysema carbon-dioxide retention may be prevented or relieved and oxygen-intake enhanced.

Morgan, P., Sherwood, N. P., and Werder, A. A.: Studies on anaphylactic shock in the mouse. J. Immunol., 79:46 (July) 1957.

A water-in-oil emulsion of bovine albumin and killed M. butyricum fatally sensitized mice.

Uri, J., Szathmary, S., and Herpay, Z.: Antibiotic production by dermatophytes in their natural habitat. J. Pharmazie, 12:485 (Aug.) 1957.

Fungi in the skin may cause penicillin reactions by actually producing penicillin.

Spielman, A. D.: Evaluation of a new antihistamine. N. Y. State Med. J., 57:3329 (Oct. 15) 1957.

Favorable report of studies of the effect of Theruhistin (Ayerst) on 84 patients.

Steffen, C. G., Mihan, R., and Zimmerman, M.: The evaluation of various antihistamines as local anesthetic agents. J. Invest. Dermat., 29:7 (July) 1957.

For patients allergic to, or not anesthetized locally by, procaine, tripelennamine (Pyribenzamine), diphenydramine (Benadryl), pyranisamine (Neo-antergan) or chlorprophenpyridamine maleate (Chlor-Trimeton) one per cent may be substituted.

Jandl, J. H., Jones, A. R., and Castle, W. B.: The destruction of red cells by antibodies in man. I. Observations on the sequestration and lysis of red cells altered by immune mechanisms. J. Clin. Invest., 36:1428 (Oct.) 1957.

The steps by means of which erythrocytes are destroyed by immunological methods are given in schematic form.

Welsh, A. L., and Ede, M.: Experience with benactyzine hydrochloride (Suavitil) in dermatologic practice. A.M.A. Arch. Dermat., 76:466 (Oct.) 1957.

Side effects noted in patients with known or suspected allergy precludes general use.

Council on Drugs, A.M.A.: Blood dyscrasias associated with promazine hydrochloride therapy. J.A.M.A., 165:685 (Oct. 12) 1957.

Four of the eighteen known cases died. The drug should be discontinued if there is sore throat, fever or malaise.

Goldman, L., and Preston, R. H.: Reactions to chloroquine observed during the treatment of various dermatologic disorders. Am. J. Trop. Med. Hyg., 6:654 (July) 1957.

With prolonged use of the drug (250-750 mg/day), anorexia, nausea, weight loss, nervousness and difficulty in accommodation occur.

Porter, H. M.: Immunologic studies in congenital agammaglobulinemia with emphasis on delayed hypersensitivity. Pediatrics, 20:958 (Dec.) 1957.

Hypersensitivity of the delayed type occurs and is probably responsible for immunity in morbilli and varicella. Circulating antibodies of gamma globulin type not produced.

Cameron, J.: The effect of aspirin, cortisone and other compounds on susceptibility to anaphylactic shock in mice. Brit. J. Exp. Path., 38:512 (Oct.) 1957.

None protect.

Osler, A. G., Hawrisiak, M. M., Ovary, Z., Siqueira, M., and Bier, O. G.: Studies on the mechanism of hypersensitivity phenomena. II. The participation of complement in passive cutaneous anaphylaxis of the albino rat. J. Exper. Med., 106:811 (Dec.) 1957.

The reaction depends on the three varying functions of antigen, antibody and a complement-resembling constituent of serum.

Mills, C. A., and Porter, M. M.: Tobacco smoking, motor exhaust fumes, and general air pollution in relation to lung cancer incidence. Cancer Res., 17:981 (Nov.) 1957.

Smoke furiously while driving slowly in a large city for a long period of time and you've had it!

Sadusk, Jr., J. F., and Nesche, G.: Influenza vaccine, Asian strain. California Med., 87:301 (Nov.) 1957.

Of 327 hospital employes, local reactions occurred in 29.1 per cent of men, 35.7 per cent of women; as chills, fever, pain, nausea, vomiting, and aching. Systemic reactions in 3.6 per cent of men, 8.8 per cent of women.

Batson, R., Christie, A., and Mazur, B.: Antibody response of the very young infant to poliomyelitis vaccine. Quart. Rev. Pediat., 12:211 (Nov.) 1957.

Can be given with other antigens. Effective in infants as young as six weeks.

Malloy, C. J.: Xiphidynia as a concomitant of asthma. Canad. M.A.J., 77:585-587 (Sept. 15) 1957.

Pressure on the xiphoid reproduced pain and occasionally asthma in the first patient and pain only in the second of two patients studied. Xiphidynia is a concomitant rather than a cause of asthma, and asthma is a concomitant rather than a cause of xiphidynia.

Finland, Maxwell: Current concepts in therapy. Antibiotics. I. General considerations and range of activity. New England J. Med., 258:85 (Jan. 9) 1958.

Good review.

Mota, I.: Action of anaphylactic shock and anaphylatoxin on mast cells and histamine in rats. Brit. J. Pharmacol., 12:453 (Dec.) 1957.

"Probably nearly all the histamine liberated in anaphylaxis in rats comes from the mast cells."

Versteegh, R. M., and Swierenga, J.: "Upper Infection" in chronic bronchitis. Nederl. tjdschr. geneesk., 101:1434 (Aug. 3) 1957 (In Dutch)

Infectious coryza and sinusitis are not sources of chronic bronchitis but merely indicate the state of the upper respiratory tract. Treatment will not favorably affect the chronic bronchitis.

Pecora, D. V., and Yegian, D.: Bacteriology of lower respiratory tract in health and chronic disease. New England J. Med., 258:71 (Jan. 9) 1958.

Careful antemortem studies prove the bronchi and lungs to be sterile in chronic diseases of the respiratory tract previously thought to be due to pyogenic infection.

# In Memoriam

### JEROME S. FRANKEL, M.D.

Dr. Jerome S. Frankel of Cleveland, Ohio, died on June 1, 1958, at the age of forty-five. He is survived by his wife, Ann, sons Mark and Robert, and daughter Susan. He was a graduate of Western Reserve University, Ohio State, and Ohio State Medical School.

Dr. Frankel was a Founding Member of the American Board of Clinical Chemistry, and a Fellow of the American Academy of Allergy, as well as a Diplomate of the American Board of Internal Medicine. He was former Director of Medical Education at Mt. Sinai Hospital in Cleveland. Dr. Frankel was elected to Fellowship in The American College of Allergists in 1952.

### LEO HOCHFELD, M.D.

Dr. Leo Hochfeld of the Bronx, New York City, died on June 30, 1957, at the age of forty-eight. Dr. Hochfeld received his medical degree from the University of Maryland in 1937. He was adjunct in allergy at Beth David Hospital, associate attending pathologist at Morrisania Hospital, and assistant attending physician in allergy at Lebanon Hospital.

He was a member of the American Academy of Allergy, the American Society of Clinical Pathologists, the New York Allergy Society, the Bronx County Medical Society, and the Medical Society of the State of New York.

Dr. Hochfeld was elected to Fellowship in The American College of Allergists in 1947.

### T. HARRY SAFERSTEIN, M.D.

Dr. T. Harry Saferstein of St. Joseph, Missouri, died on July 28, 1958, at the age of fifty-two. Dr. Saferstein graduated from the University of Kansas School of Medicine in 1930 and interned at the Broadlawns Hospital of Des Moines, Iowa. He was resident physician at the Menorah Medical Center in Kansas City, Missouri.

Dr. Saferstein was a member of the Buchanan County Medical Society, the Southern Medical Association, and the American Academy of Allergy. He was on the staff of St. Joseph's Hospital, Missouri Methodist Hospital, and the Missouri State Hospital, all of St. Joseph, Missouri. He served as a Lieutenant Commander in the U. S. Navy during World War II.

Dr. Saferstein became an Associate Fellow of The American College of Allergists in 1954.

### LEWIS E. SHREWSBURY, M.D.

Lewis E. Shrewsbury, M.D., of Beckley, West Virginia, died on June 22, 1958. He is survived by his wife, Fernia, two daughters, Fernia Rose and Mrs. Martha Gates, a son, Lewis, Jr., and one brother, James.

Dr. Shrewsbury graduated from the University of Louisville Medical School in 1914, and interned at City Hospital, Louisville, Kentucky.

He served as President of the Raleigh County Medical Society in 1936, and was a member of the Southern Medical Association, West Virginia Medical Association, and National Allergy Association. He became an Associate Fellow of The American College of Allergists in 1947.

IN MEMORIAM

**ROBERT B. SMITH, M.D.**

Dr. Robert B. Smith of Akron, Ohio, died on February 2, 1958. He is survived by his wife, a daughter, and two sons.

Dr. Smith received his degree from Ohio State University School of Medicine in 1940. He was a diplomate of the American Board of Internal Medicine, Fellow of the American College of Physicians, and a member of the American Academy of Allergists and the American Heart Association.

He was Chief of the Department of Medicine of St. Thomas Hospital and a member of the Senior Attending Staff of the City Hospital, of Akron, Ohio.

Dr. Smith was elected to Fellowship in The American College of Allergists in 1946.

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# News Items

## SECTION ON ALLERGY OF THE NERVOUS SYSTEM

The Section on Allergy of the Central Nervous System is anxious to present a stimulating and provocative program for the next meeting of the College in San Francisco. The psychological and peripheral disturbances resulting from atopic or other types of allergy are of interest to all members of our organization. Suggestions from any members of the College about possible contributions from either the clinical or experimental viewpoint will be appreciated. The influence of various drugs and bio-chemical agents on the central nervous system is receiving increasing attention. The by-products of the allergic reaction may also play a part in mental or emotional changes. We need your ideas and help.

## AMERICAN COLLEGE OF CHEST PHYSICIANS

The twenty-fourth annual meeting of the American College of Chest Physicians was held at the Fairmont Hotel, San Francisco, June 18-22, 1958. Fellowship certificates were presented to 160 physicians.

Dr. J. Winthrop Peabody, Washington, D. C., Professor Emeritus, Diseases of the Respiratory System, Georgetown University School of Medicine, was awarded the 1958 College Medal for his meritorious achievements in the specialty of diseases of the chest, particularly in the field of postgraduate medical education.

The following officers were elected for the year 1958-1959:

President.....Donald R. McKay, Buffalo, New York
President-Elect.....Seymour M. Farber, San Francisco, California
First Vice-President.....M. Jay Flipse, Miami, Florida
Second Vice-President.....Hollis E. Johnson, Nashville, Tennessee
Treasurer .....Charles K. Petter, Waukegan, Illinois
Assistant Treasurer.....Albert H. Andrews, Chicago, Illinois
Chairman, Board of Regents.....John F. Briggs, St. Paul, Minnesota
Historian.....Carl C. Aven, Atlanta, Georgia

## CURRENT CONTENTS

Sample copies of *Current Contents,* which lists the Tables of Contents of contemporary medical journals, may be obtained at no cost by the readers of the ANNALS by writing to Mr. Eugene Garfield, Editor and Publisher, 1523 Spring Garden Street, Philadelphia 30, Pennsylvania.

## SOUTHEASTERN ALLERGY ASSOCIATION

The Southeastern Allergy Association will hold its annual meeting on October 31 and November 1, 1958, at the Heart of Atlanta Motel, Atlanta, Georgia. All interested persons are cordially invited to attend.

## NEWS OF MEMBERS

Mayer A. Green, M.D., F.A.C.A., has been appointed Chief of the Division of Allergy, Department of Medicine, at Montefiore Hospital in Pittsburgh, Pennsylvania.

## NOTICE OF ELECTION OF OFFICERS AND REGENTS
## THE AMERICAN COLLEGE OF ALLERGISTS

The Nominating Committee has selected one candidate for each elective office to be voted on at the next annual election in accordance with the By Laws of The American College of Allergists, Article V, Section 7( j), which reads as follows:

"Article V, Section 7 (j).—The Nomination of Officers.—The Nominating Committee shall be composed of five (5) members: The President, two (2) members of the Board of Regents each of whom has served at least two (2) years on the Board, and two (2) Past Presidents, both Regents and Past Presidents to be selected by the Board. *No member may serve on this committee for two consecutive years.* Not earlier than three (3) months, but not more than six (6) months after its selection, the Nominating Committee shall pick one (1) candidate for each elective office and this shall be known as the official ballot. In making its selection, it shall take into consideration the qualifications, fitness, capacity, standing, and accomplishments in the field of allergy of those considered for selection, and all information contained in the membership records maintained in the Treasurer's office as to any proposed selectees shall be seasonably supplied to the committee for this purpose. The Nominating Committee shall report its selections to the Treasurer's office and as soon as convenient thereafter, but not less than three (3) months before the ensuing election, notice of this official ballot shall be given to all voting Fellows of the College. This notice may be given either by publication thereof in the official organ of the College, ANNALS OF ALLERGY, or by mail. Additional nominations may also be made by petition, signed by ten (10) Fellows and sent to the office of the Secretary, provided said additional nominations are received in the office of the Secretary at least thirty (30) days prior to the next annual meeting. Nominations may also be made from the floor at any annual meeting. The election of officers and Regents shall be by ballot and shall be by a majority of the votes cast at the annual meeting."

*Nominating Committee*

MERLE W. MOORE, *Chairman*
SAM H. SANDERS
WILLIAM C. SERVICE
J. WARRICK THOMAS
ORVAL R. WITHERS

OFFICIAL BALLOT

President-Elect.....GILES A. KOLLSCHE
First Vice President.....PHILIP M. GOTTLIEB
Second Vice President.....WILLIAM B. STEEN
Secretary.....MERYL M. FENTON
Board of Regents (Three-Year Term).....R. DALE DICKSON
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# BOOK REVIEWS

IMMUNOPATHOLOGIE IN KLINIK UND FORSCHUNG UND DAS PROBLEM DER AUTOANTIKöRPER (Immunopathology in clinic and research and the problem of anti-antibodies). Edited by P. Miescher, Basel, and K. O. Vorlaender, Bonn. Stuttgart (Germany) 1957, Georg Thieme Verlag. 598 pages, 119 figures. Price, $16.45.

Beyond the pale of the recognized "immunological" diseases (eg. classical "allergies" and the disturbances connected with the group specificities of the erythrocytes) there is a growing borderland of pathology, where evidence of the etiological role of immunological mechanisms is accumulating. This borderland is the main theme of the present textbook, which thus covers a field not systematically presented in any language to this reviewer's knowledge.

Following an outstandingly well written introductory chapter on Basic Immunology (by Pierre Grabar of Paris) and a short chapter on anti-erythrocytic antibodies, the available experimental data on antibody reactions against leukocytes, thrombocytes, kidney and liver tissues, the muscular and connective tissues and the nervous system are presented.

The second and much larger moiety of the book is employed for a comprehensive presentation of the immunological aspects of the following diseases and disease groups: hemolytic anemias, agranulocytoses, thrombopenias (and purpurae), nephritis, liver and rheumatic affections, diseases of the thyroid gland, the complex of lupus erythematosus, neurological affections, ophthalmias, and finally on the problems of homotransplantation. Of exceptional quality are those chapters authored or co-authored by P. Miescher. Many techniques not otherwise conveniently brought together are described in detail. Ample reference lists are appended to each chapter.

A considerable part of the work has been done by workers who do not habitually publish in English or American periodicals. That the work of these authors is amply presented and the references given is a most welcome feature of this book.—A.J.W.

MANAGEMENT OF THE PATIENT WITH HEADACHE. Perry S. MacNeal, M.D., Bernard J. Alpers, M.D., and William R. O'Brien, M.D. 145 Pages, including index. Philadelphia: Lea and Febiger, 1957. Price, $3.50.

This interesting little book contains a good deal of information. Both vascular and non-vascular types of headache are discussed, and considerable space is devoted to differential diagnosis.

The book seems, however, to be written primarily from the psychodynamic point of view. Personality and emotional factors are overemphasized. In the mind of the reviewers other factors should have warranted more discussion. Other books on headache (both for physicians and laymen) have also shown the same emphasis. We must all recognize that headache may be due to a multiplicity of causes.

The authors do make a statement with which the reviewer is in complete accord, "The notorious tendency for patients with migraine and tension headache to notice temporary improvement from any medication which is administered in a scientific atmosphere and mixed with elixir of the physician's own enthusiasm may be responsible for much of the reported improvement." They also state that routine skull x-rays and spinal punctures should not be done. The reviewer agrees that such diagnostic procedures are not indicated in many cases, however any possible

causes of headache should be thoroughly investigated and all too often the patient with severe recurrent headache has not had the benefit of a comprehensive study.

The authors associate allergic headache with histamine cephalalgia, and emphasize the importance of sensitivity to food in this disorder. They state that "Skin testing is not helpful in detecting these food allergens." While there is a difference of opinion among allergists on this point, it does seem to the reviewer that in some cases, skin testing for foods may be helpful. All allergists are aware of the frequency of the frontal type of headache, which is often associated with inhalant sensitizations. This topic has been ignored. However, in spite of this, the book is worth reading by physicians interested in headaches.—H.D.O.

ANNUAL REVIEW OF MEDICINE. David A. Rytand, Editor; Willliam Creger, Associate Editor. Volume 8. 530 pages, including indexes. Palo Alto, California: Annual Reviews, Inc., 1957. Price $7.00 (U.S.A.), $7.50 (elsewhere).

If the reviewer were limited in his reading to one book yearly he would, without any doubt whatsoever, choose the Annual Review of Medicine. For eight years, each volume has been as good as the preceding volumes in the choice of its contributors and the excellence of their contributions.

In the eighth volume of the series there is a chapter on Adrenocortical Hormones and the Management of Infection by Kass and Finland, and another on Allergy and Immunology by David W. Talmage. There is a review on the Physics and Chemistry of Dust by C. N. Davies and on Diseases of the Respiratory System by J. B. Amberson. The former deals with inorganic dusts and the latter with chronic disorders nonallergic in origin. There is a short but excellent chapter by Bunin and Block on the Collagen Diseases and a rewarding review on Psychiatry by Stewart Wolf.

The internist interested in allergy may not want to spend much time on Diseases of the Gastrointestinal Tract or on Medical Diseases of the Kidney or on Obstetrics, but the book, since it reviews recent advances in all of the fields of medicine, must include them. These and other chapters outside our specialty are worth a quick reading.

It is to be regretted that one of the most important features of the Annual Review, namely, the Annotated List of Reviews in Medicine by E. M. and L. McKay was omitted for "lack of space."

The ninth volume (in preparation) lists chapters on Allergy and Immunology by F. J. Dixon, Psychiatry by R. A. Cleghorn, Special Therapeutics by L. Lasagna, and Diseases of the Skin by S. Rothman and L. Lorincz. It promises to make as exciting reading as does the eighth volume.

UNEXPECTED REACTIONS TO MODERN THERAPEUTICS—ANTIBIOTICS. Leo Schindel, M.D. 146 pages, including index. Illinois: Charles C Thomas Publisher, 1957. Price: $3.00.

If the mortality trends of 1937, the year sulfonamides were first used, were extrapolated to 1957, then 1,000,000 more people would have died of pneumonia, 76,000 women of puerperal sepsis, 90,000 patients of appendicitis, and 136,000 patients of syphilis. But the curve is becoming flat. There are other causes than the use of the antibacterial agents for the lessened morbidity and mortality of a number of infectious disorders, and they in their own right are becoming increasingly causes of drug-induced disorders and death.

To listen to the manufacturers' representatives, every new drug is more efficacious than its predecessors. It is generally "acclaimed" until within months and sometimes years, its ill effects directly as on the patient or indirectly as with resistance to antibiotic agents are recognized as the causes of disease.

It would ease the conscience of physicians if, as Doctor Schindel states in the Introduction to his book, the doctor could "console himself that not he but rather the patient's hypersensitivity was actually responsible for the undesirable reaction." He says, however, that it would be wrong to assume that hypersensitivity alone is responsible for the side effects observed with medicaments.

The author's knowledge of specific toxic effects is wide. He quotes the regular development of cataracts in hens given dinitrophenol and of granulocytopenia in rats given succinysulphthazole.

Of interest is his discussion of Beecher's work with placebos; a study in which 35.2 per cent of 1,082 subjects improved, but side effects as dryness of the mouth, nausea, headache, fatigue, difficulty in concentrating and somnolence were noted. Wolf and Pinsky studies the side effects of placebo medications. Listed among others are nausea, tachycardia, excessive perspiration and pruritic maculopapular erythematous rashes; epigastric distress, diarrhea, angioedema and urticaria. It is for this reason that it is sometimes difficult to distinguish between "true" and "false" side effects. The author has steered his difficult course between these extremes.

Separate chapters describe the reactions to penicillin, the streptomycins, chloramphenicol, the tetracyclines, neomycin, erythromycin, bacitracin, fumagillin, novobiocin, cycloserine and polymyxin. One chapter concerns antibiotic-resistant bacteria. A postscript discusses the attitude a physician should take towards a new drug.

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